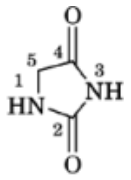
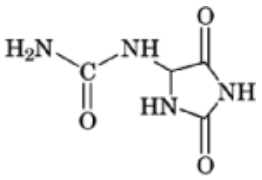
Kirk-Othmer Encyclopedia of Chemical Technology.

HYDANTOIN AND ITS DERIVATIVES

Hydantoin (**1**) is an accepted name for 2,4-imidazolidinedione [461-72-3]. This ring system rarely occurs in nature, although some natural products with hydantoin substructures are known. For example, allantoin [97-59-6] (**2**) is a constituent of urine and axinohydantoin [125143-99-9] (**3**) is an antitumor component of Indo-Pacific marine sponges (1). Hydantoin itself was synthesized by Baeyer in 1861, although its structure was not assigned correctly until 1870 by Strecker. A huge number of derivatives have been prepared since then, among which several 5,5-disubstituted derivatives have found use in medicine. Other applications of hydantoin derivatives include their use as synthetic and analytical reagents, and a variety of sanitary, agricultural, industrial, and other uses. The chemistry of hydantoins has been reviewed (2–5). A review of thiohydantoins is also available (6).



(**1**)



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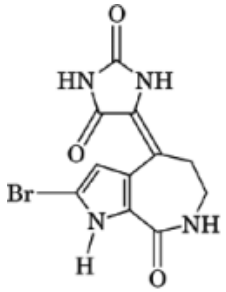


(**3**)

Table 1. Melting Points of Some Hydantoin Derivatives[a]

R	R″	Mp, °C
H	H	214–220[b,c]
CH_3	H	178–182.5[d]
C_6H_5	H	295–299
C_6H_5	CH_3	216–217
CH_2CH_3	CH_3	138
H	CH_2CH_3	94
CH_2CH_3	H	198

[a] R′ = phenyl (C_6H_5) unless otherwise noted.
[b] R′ = H.
[c] Literature values vary, depending on the rate of heating.
[d] R′ = CH_3.

1. Physical Properties

Hydantoins are crystalline solids with high melting points, particularly those compounds in which nitrogen is unsubstituted, because this allows intermolecular association by hydrogen bonds (Table 1). Hydantoins are weak acids, which dissociate at the imidic N-3—H atom because this allows more efficient delocalization of the negative charge than ionization at N-1. Definite proof for the nonacidic character of the latter position comes from the fact that 3-substituted hydantoins show no appreciable ionization (7).

Several structure—acidity relationships have been established for hydantoin derivatives. Thus, ionization is known to be unaffected by alkyl substituents at N-1 and at C-5; for example, pK_a of hydantoin is 9.0 and that of 1-methylhydantoin is 9.1 (8). However, aryl and other electron-withdrawing groups can considerably enhance the acidity of hydantoins; thus 5,5-diphenylhydantoin [57-41-0] (phenytoin) has a pK_a of 8.12 (9), and 1-benzenesulfonyl-5,5-diphenylhydantoin [21413-28-5] has a pK_a of 4.89 (10). Introduction of an arylmethylene side chain at C-5 increases the acidity of the N-1 hydrogen, making it measurable (11). This is due to delocalization of the negative charge at N-1 into the C-5 substituent.

Solvent variation can greatly affect the acidity of hydantoins. Although two different standard states are employed for the pK_a scale and therefore care must be exercised when comparing absolute acidity constants measured in water and other solvents like dimethyl sulfoxide (DMSO), the huge difference in pK_a values, eg, 9.0 in water and 15.0 in DMSO (12) in the case of hydantoin itself, indicates that water provides a better stabilization for the hydantoin anion and hence an increased acidity when compared to DMSO.

2-Thiohydantoin [503-87-7] (pK_a 8.5) is a slightly stronger acid than hydantoin (pK_a 9.0). 4-Thiohydantoins appear to be weaker acids (4).

2. Spectral Properties

Hydantoin derivatives show weak absorption in the uv-visible region, unless a part of the molecule other than the imidazolidinedione ring behaves as a chromophore (13); however, pK_a values have been determined by spectrophotometry in favorable cases (14). Absorption of uv by thiohydantoins is more intense, and the two bands observed have been attributed to $n \longrightarrow \pi*$ and $n \longrightarrow \sigma*$ transitions of the thiocarbonyl group (15, 16). Several pK_a values of thiohydantoins have been determined by uv-visible spectrophotometry (16).

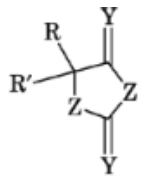
Infrared spectra of hydantoins show two characteristic carbonyl absorptions at about 1720 and 1780 cm^{-1}. Assignment of these bands has been controversial, and the low frequency signal has been attributed both to C-4 and C-2 carbonyls. In an alternative interpretation, these bands have been assigned (17) to symmetrical and asymmetrical vibrations of a coupled carbonyl system similar to the one found in imides. The relative intensities

of both bands can be used as a criterion for structural studies on hydantoins, such as hydrogen bonding (18) and the absence of oxo–enol tautomerism in hydantoins (19). Bands due to N—H stretching vibrations give rise to complex absorption patterns in the 3000–3500 cm^{-1} region, depending on the degree of molecular association by hydrogen bonds (18, 20, 21)

^{1}H-nmr chemical shifts of N-1—H and N-3—H signals have been used as a criterion for distinguishing between N-1-substituted and N-3-substituted hydantoin derivatives (22). They can often be related to electronic properties, and thus good linear correlations have been found between the shifts of N—H and Hammett parameters of the substituents attached to the aryl group of 5-arylmethylenehydantoins (23).

^{13}C-nmr data have been recorded and assigned for a great number of hydantoin derivatives (24). As in the case of ^{1}H-nmr, useful correlations between chemical shifts and electronic parameters have been found. For example, Hammett constants of substituents in the aromatic portion of the molecule correlate well to chemical shifts of C-5 and C-α in 5-arylmethylenehydantoins (23). Comparison between ^{13}C-nmr spectra of hydantoins and those of their conjugate bases has been used for the calculation of their pK_a values (12, 25). ^{15}N-nmr spectra of hydantoins and their thio analogues have been studied (26). The ^{15}N-nmr chemical shifts show a linear correlation with the frequencies of the N—H stretching vibrations in the infrared spectra.

Luminescence spectra of hydantoin have been compared (27) with those of related heterocycles, represented by the **following structure**. The spectra are more sensitive to variation in the exocyclic heteroatoms (Y) rather than the endocyclic ones (Z).



Y = O, S; Z = O, NH

Mass spectral fragmentation patterns of alkyl and phenyl hydantoins have been investigated by means of labeling techniques (28–30), and similar studies have also been carried out for thiohydantoins (31, 32). In all cases, breakdown of the hydantoin ring occurs by α-fission at C-4 with concomitant loss of carbon monoxide and an isocyanate molecule. In the case of aryl derivatives, the ease of formation of Ar—NCO is related to the electronic properties of the aryl ring substituents (33). Mass spectrometry has been used for identification of the phenylthiohydantoin derivatives formed from amino acids during peptide sequence determination by the Edman method (34).

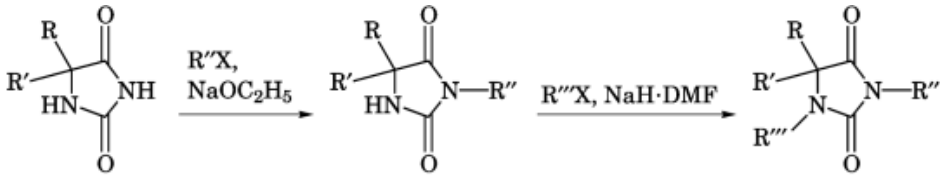
3. Chemical Properties

Hydantoins can react with electrophiles at both nitrogen atoms and at C-5. The electrophilic carbonyl groups can be attacked by nucleophiles, leading to hydrolysis of the ring or to partial or total reduction of the carbonyl system. Other reactions are possible, including photochemical cleavage of the ring.

4. Reactions at Nitrogen

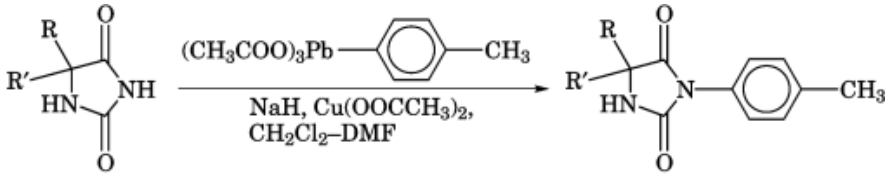
The imide proton N-3—H is more acidic than N-1—H and hence this position is more reactive toward electrophiles in a basic medium. Thus hydantoins can be selectively monoalkylated at N-3 by treatment with

alkyl halides in the presence of alkoxides (2, 4). The mono-*N*-substituted derivatives (**5**) can be alkylated at N-1 under harsher conditions, involving the use of sodium hydride in dimethylformamide (35) to yield derivatives (**6**). Preparation of N-1 monoalkylated derivatives requires previous protection of the imide nitrogen as an aminomethyl derivative (36). Hydantoins with an increased acidity at N-1—H, such as 5-arylmethylene derivatives, can be easily monoalkylated at N-3, but dialkylation is also possible under mild conditions.



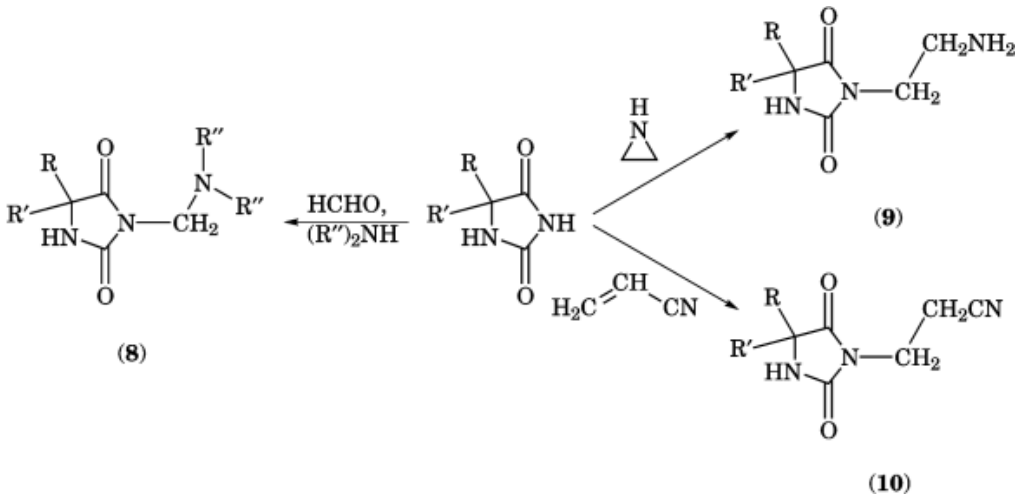
(**4**) (**5**) (**6**)

Similarly, hydantoins can be arylated at N-3. For example, treatment of 5,5-diphenylhydantoin (**4**), R = R′ = C_6H_5 (phenytoin), with *p*-tolyllead triacetate in the presence of sodium hydride and a catalytic amount of copper(II) acetate (37) gives compound (**7**).



(**4**) (**7**)

Other reactions that show preference for the acidic N-3—H group include Mannich aminomethylation by treatment with formaldehyde and an amine (38) to yield compound (**8**), reaction with ethyleneimine (39) to give (**9**), and Michael-type additions (40) such as the one with acrylonitrile to give (**10**):



(**8**) (**9**) (**10**)

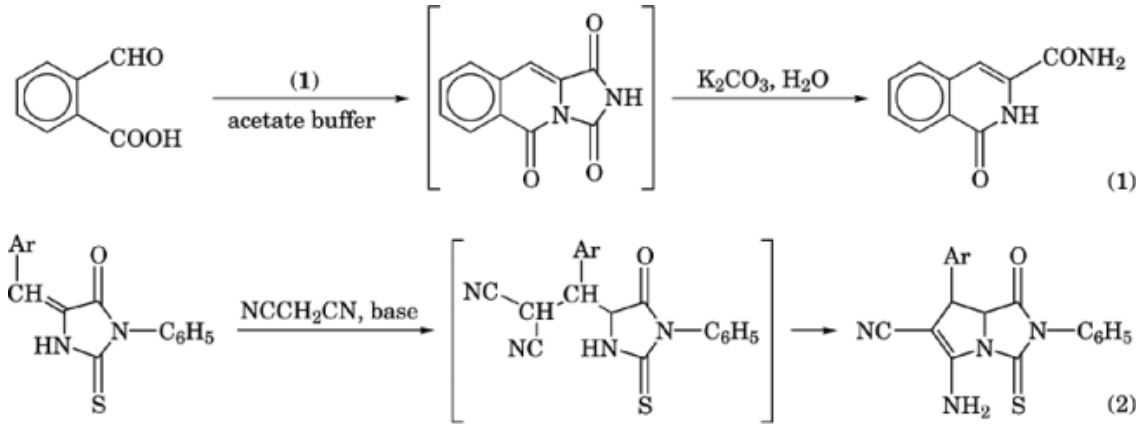
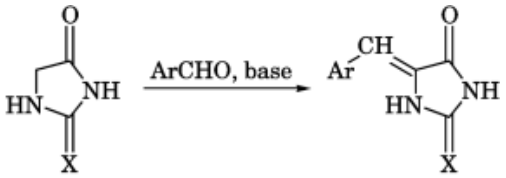


Fig. 1. 5-Substituted hydantoins as synthetic intermediates. equation **1** (45); equation **2** (46).

Several electrophiles, such as acetic anhydride, nitric acid or alternative nitrating agents, such as ammonium nitrate in trifluoroacetic anhydride (41), or sodium hypochlorite, react at N-1, which is followed by reaction at N-3 under suitable conditions. In the case of acetic anhydride, the reaction can take place exclusively at N-3 if N-1 is hindered; this fact has served as a criterion for studying the stereochemistry of 5-spirohydantoin derivatives (42, 43).

4.1. Reactions at C-5

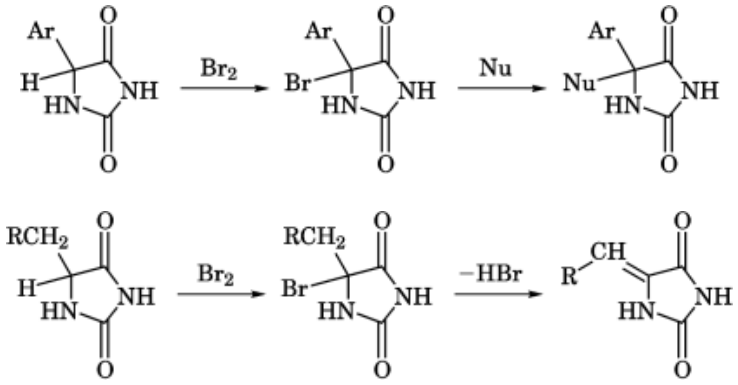
The C-5 atom of hydantoins can be considered as an active methylene group, and therefore is a suitable position for base-catalyzed condensation reactions with aldehydes (44). 2-Thiohydantoins give the reaction more readily than their oxygen counterparts:



X = O, S

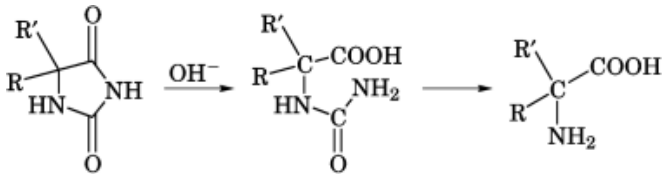
Some of the 5-arylmethylene derivatives thus obtained are useful synthetic intermediates, as shown in Figure 1

Similarly, the reaction with bromine yields the corresponding 5-bromo derivatives, which are suitable substrates for nucleophilic displacement or dehydrohalogenation reactions. Typical nucleophiles (Nu) are H_2O, NH_3, RNH_2, and sodium barbiturates:



4.2. Hydrolysis

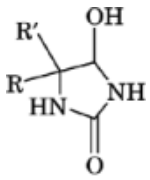
Although hydantoins can be hydrolyzed under strongly acidic conditions, the most common method consists of heating in an alkaline medium to give intermediate ureido acids (the so-called hydantoic acids), which are finally hydrolyzed to α-amino acids.



Preparation of amino acids (qv) by this sequence has traditionally been one of the main applications of hydantoins, particularly where other synthetic methods fail. Much of the research effort has been directed toward the development of enzymatic methods for the stereoselective hydrolysis of hydantoins (47). Both D-specific and L-specific hydantoinases (ie, enzymes capable of hydrolyzing hydantoins) are known, thus allowing the preparation of D- and L-amino acids. The use of these enzymes is illustrated in Figure 2 by the synthesis of D-tyrosine [556-02-5], a structural fragment of the antibiotic Amoxicillin (48).

4.3. Reduction

Lithium aluminum hydride is the most common reagent for the reduction of hydantoins. The structure of the products obtained varies, depending on reaction conditions and on the nature of the substituents at C-5, N-1, and N-3. Room temperature reductions (49, 50) usually yield 4-hydroxy-2-imidazolidinones (**11**) or the corresponding dehydration products (**12**). Reflux conditions (51, 52) give 2-imidazolidinones (**13**), imidazoles (**14**), or imidazolidines (**15**).



(**11**)

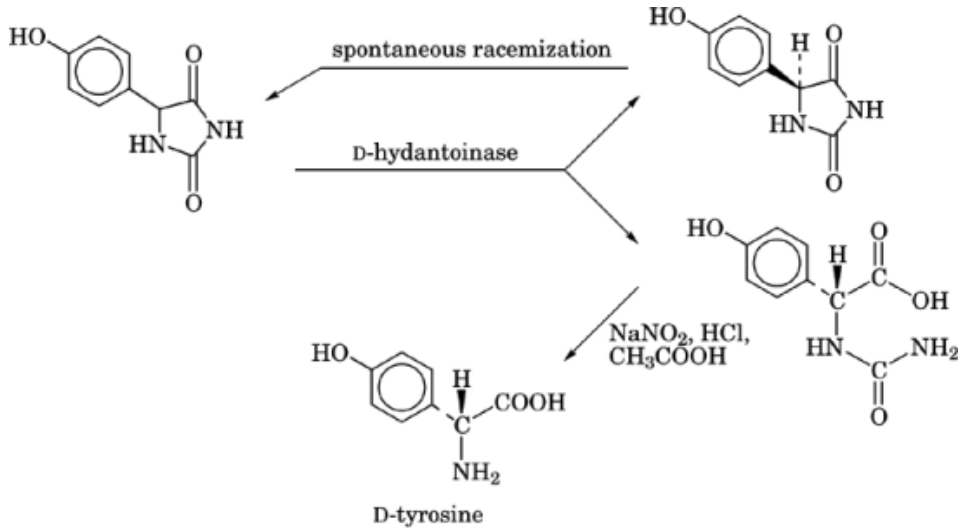
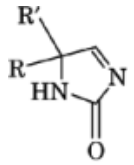
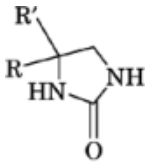


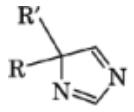
Fig. 2. Enzymatic synthesis of D-tyrosine from (±)5-(4-hydroxyphenyl)hydantoin [54832-24-5].



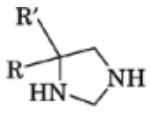
(**12**)



(**13**)

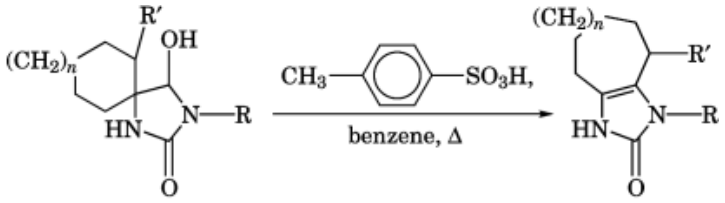


(**14**)



(**15**)

Reaction products (**11**) can rearrange under suitable conditions (53) to condensed 2(3*H*)-imidazolidinones such as (**16**):

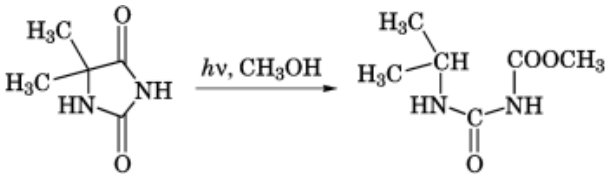


(**16**)

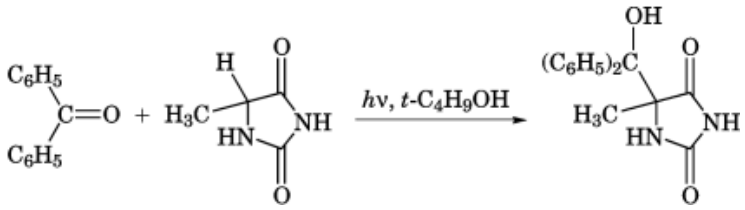
Compound (**12**) can also be obtained by dissolving metal reactions through treatment with an excess of lithium—liquid ammonia in *tert*-butyl alcohol (54).

4.4. Photochemical Reactions

Hydantoins and other heterocycles containing an NCO group suffer ring cleavage under photochemical conditions. Thus irradiation of 5,5-dimethylhydantoin [77-71-4] in methanol in the absence of benzophenone and oxygen leads to oxidative fission of the C−4—C−5 bond (55):

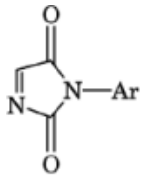


On the other hand, when a similar photoreaction is carried out on hydantoin or its 5-monosubstituted derivatives in the presence of benzophenone, the hydrogen atom at C−5—H is abstracted and the resulting radical couples with that of benzophenone (56):



4.5. Miscellaneous Reactions

Some hydantoin derivatives can serve as precursors of carbonium—immonium electrophiles (57). 5-Alkoxyhydantoins are useful precursors of dienophiles (**17**), which undergo Diels-Alder cycloadditions under thermal conditions or in the presence of acid catalysis (58). The pyridine ring of Streptonigrine has been constructed on the basis of this reaction (59).

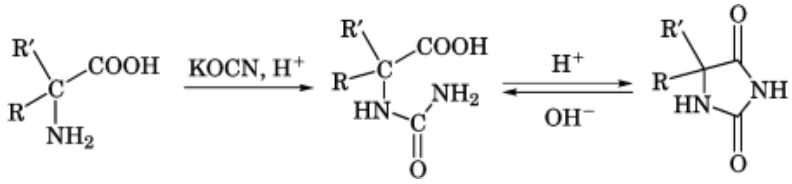


(**17**)

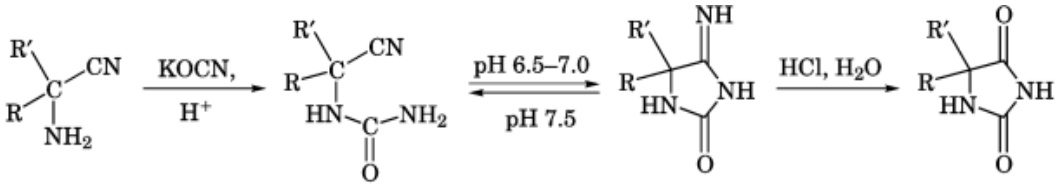
5. Synthesis

5.1. Synthesis from α-Amino Acids and Related Compounds

Addition of cyanates, isocyanates, and urea derivatives to α-amino acids yields hydantoin precursors. This method is called the Read synthesis (2), and can be considered as the reverse of hydantoin hydrolysis. Thus the reaction of α-amino acids with alkaline cyanates affords hydantoic acids, which cyclize to hydantoins in an acidic medium.



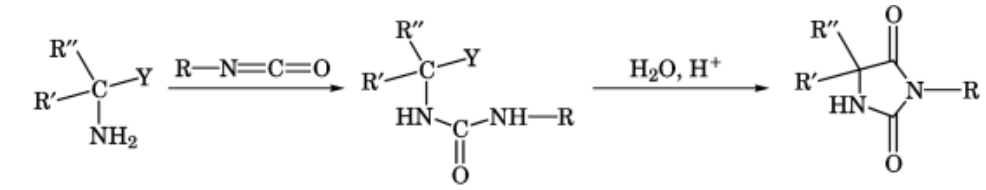
In a modification of the original method, Read (60) replaced α-amino acids with α-amino nitriles. This reaction is sometimes known as Strecker hydantoin synthesis, the term referring to the reaction employed for the synthesis of the α-amino nitrile from an aldehyde or ketone. The cyclization intermediate (**18**) has been isolated in some cases (61), and is involved in a pH-controlled equilibrium with the corresponding ureide.



(**18**)

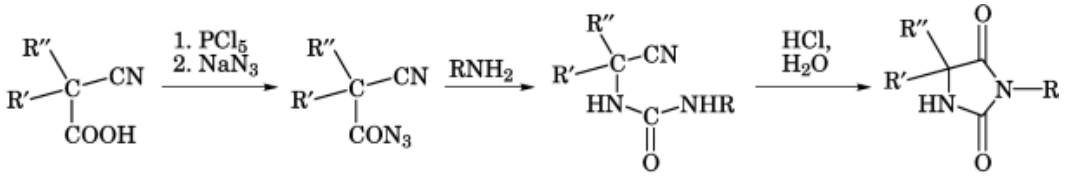
Chlorosulfonyl isocyanate is an excellent alternative to alkaline cyanates in the preparation of hydantoins from sterically hindered or labile amino nitriles (62). Imino derivatives similar to (**18**) can also be obtained by addition of sonitriles to imines followed by treatment with a cyanate (63).

Substitution of alkaline cyanates by isocyanates allows the preparation of 3-substituted hydantoins, both from amino acids (64) and amino nitriles (65). The related reaction between α-amino acids and phenyl isothiocyanate to yield 5-substituted 3-phenyl-2-thiohydantoins has been used for the analytical characterization of amino acids, and is the basis of the Edman method for the sequential degradation of peptides with concomitant identification of the *N*-terminal amino acid.

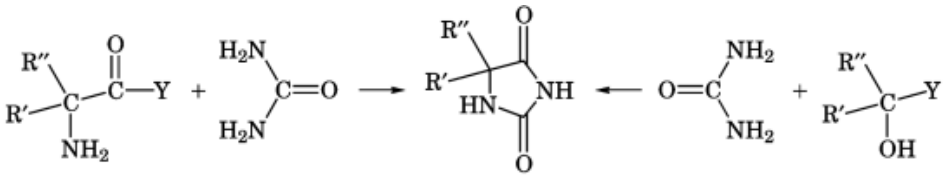


Y = CN, COOH

A related reaction sequence, which proceeds through a Curtius rearrangement, allows the transformation of α-cyano acids into hydantoins (66):



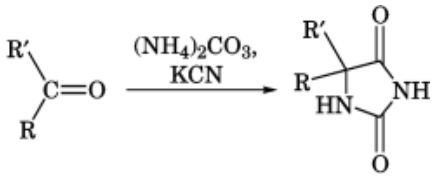
A variety of α-amino acid derivatives, including the acids themselves, halides, esters, and amides can be transformed into hydantoins by condensation with urea (67). α-Hydroxy acids and their nitriles give a similar reaction (68):



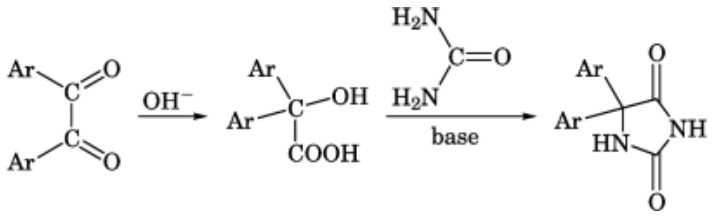
Y = OH, Cl, OR, NH_2 Y = CN, COOH

5.2. Synthesis from Aldehydes and Ketones

Treatment of aldehydes and ketones with potassium cyanide and ammonium carbonate gives hydantoins in a one-pot procedure (Bucherer-Bergs reaction) that proceeds through a complex mechanism (69). Some derivatives, like oximes, semicarbazones, thiosemicarbazones, and others, are also suitable starting materials. The Bucherer-Bergs and Read hydantoin syntheses give epimeric products when applied to cycloalkanones, which is of importance in the stereoselective synthesis of amino acids (69, 70).

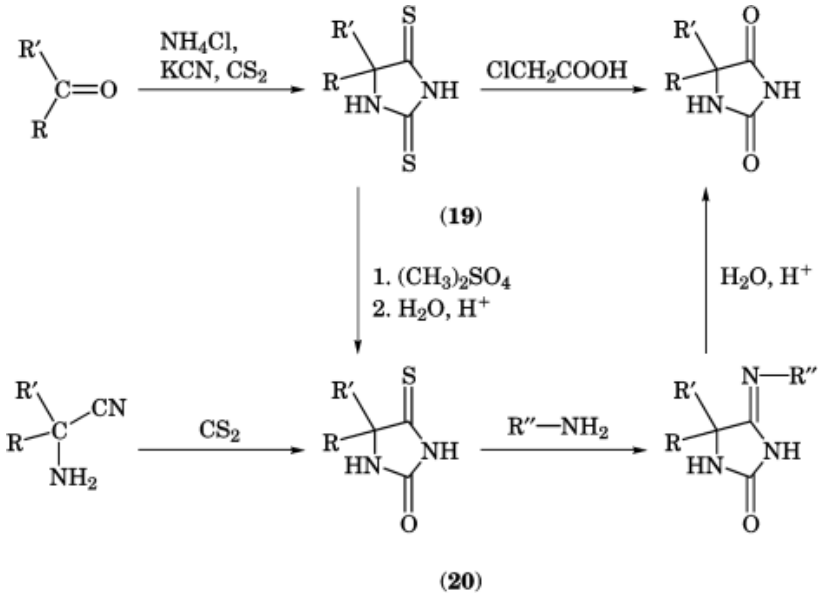


Treatment of α-dicarbonyl compounds with urea in a basic medium is a good method for the synthesis of 5,5-disubstituted hydantoins. This reaction is particularly useful for 5,5-diaryl derivatives, difficult to obtain by the Bucherer-Bergs method. It involves a benzylic rearrangement of the starting compound to an α-hydroxy acid, followed by cyclization of the latter:



5.3. Synthesis from Thiohydantoins

A modification (71) of the Bucherer-Bergs reaction consisting of treatment of an aldehyde or ketone with carbon disulfide, ammonium chloride, and sodium cyanide affords 2,4-dithiohydantoins (**19**). 4-Thiohydantoins (**20**) are available from reaction of amino nitriles with carbon disulfide (72). Compounds (**19**) and (**20**) can be transformed into hydantoins.



(**20**)

6. Analytical and Test Methods

Hydantoin itself can be detected in small concentrations in the presence of other NH-containing compounds by paper chromatography followed by detection with a mercury acetate—diphenylcarbazone spray reagent. A variety of analytical reactions has been developed for 5,5-disubstituted hydantoins, due to their medicinal interest. These reactions are best exemplified by reference to the assays used for 5,5-diphenylhydantoin (73–78), most of which are based on their cyclic ureide structure. Identity tests include the following: (*1*) the Zwikker reaction, consisting of the formation of a colored complex on treatment with cobalt(II) salts in the presence of an amine; (*2*) formation of colored copper complexes; and (*3*) precipitation on addition of silver(I) species, due to formation of insoluble salts at N_3.

An acidimetric quantitative determination is based on treatment of the hydantoin with silver nitrate and pyridine in aqueous solution. Complexation of the silver ion at N-3 liberates a proton, and the pyridinium ions thus formed are titrated using phenolphthalein as an indicator. In a different approach, the acidity of N-3—H is directly determined by neutralization with tetrabutylammonium hydroxide or sodium methoxide in dimethylformamide.

A review published in 1984 (79) discusses some of the methods employed for the determination of phenytoin in biological fluids, including thermal methods, spectrophotometry, luminescence techniques, polarography, immunoassay, and chromatographic methods. More recent and sophisticated approaches include positive and negative ion mass spectrometry (80), combined gas chromatography—mass spectrometry (81), and ftir immunoassay (82).

7. Health and Safety Factors (Toxicology)

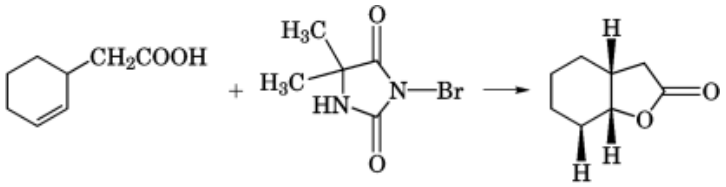
The acute toxicity of hydantoin derivatives seems to be low. Most studies on long-term toxicity of hydantoins deal with phenytoin, due to the wide use of this compound as an anticonvulsant (83). Long-term toxic effects of phenytoin include folate deficiency due to impaired folate absorption, hypocalcemia and osteomalacia, alterations of carbohydrate metabolism, gingival hyperplasia, and teratogenic effects. These are grouped under the term fetal hydantoin syndrome, which is associated with continued use of hydantoins during the early stages of pregnancy, and consists of mild retardation of physical and mental indexes, dysmorphic faces and, occasionally, cleft palate, cleft lip, and cardiac defects.

Formation of cyanide by degradation of hydantoin derivatives used as antiseptics for water treatment has been described (84), and this fact might have toxicological relevance.

8. Applications

8.1. Halogenated Hydantoins

Halogenation has been achieved by use of a variety of halogenating reagents (2, 85). These derivatives are employed as reagents in synthesis and analysis and also as disinfectants and biocides in water treatment. In synthesis, 3-bromohydantoins are equivalents of *N*-bromosuccinimide and other *N*-bromoamides, acting as a source of halogen for selective allylic and benzylic bromination (86). Among other reactions, both 3-bromo- and 3-iodohydantoins are very convenient reagents for halolactonization of unsaturated carboxylic acids (87):



In analysis, 1,3-dihalohydantoins can be used as oxidimetric titrants for determining hydrazine and phenylhydrazine, thiourea, hydroquinone, ascorbic acid, quinoline derivatives such as primaquine, chloroquine, amodiaquine, quinidine and quinine, phenothiazines such as chlorpromazine, Sb(III), As(III), Sn(II), Fe(II), Tl(I), $Fe(CN)^{4-}_6$, I^-, SCN^-, Ti(III) etc (88–91) Other hydantoins and thiohydantoins have been used as analytical reagents for heavy metals because of their capacity for complex formation (92–94).

Halohydantoins, particularly 1,3-dichloro-5,5-dimethylhydantoin [118-52-5] (commercially available under the name of Dichlorantin) and 1-bromo-3-chloro-5,5-dimethylhydantoin [16079-88-2], ensure high disinfecting and bactericidal effects in water-purification plants, because they are capable of producing hypohalite ions (see Chloramines and bromamines). They can also be used in sanitizing and bleaching toilet bowls, as disinfectants for dental appliances, for automatic dishwashers, as resin stabilizers, etc. Agglomerated halohydantoins releasing active halogen at a controlled rate have been patented (95–97).

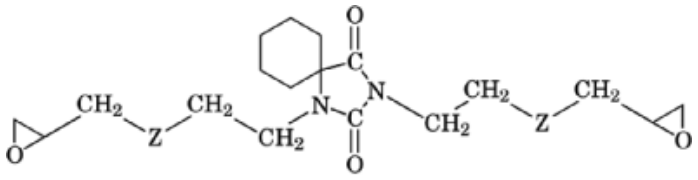
8.2. *N*-Methylolhydantoins

1,3-Bis(hydroxymethyl)-5,5-dimethylhydantoin [6440-58-0] is used extensively as a preservative in cosmetic and industrial applications, and carries EPA registration for the industrial segment. It is available in solid and in aqueous solution forms, including low free formaldehyde versions of the latter. A related derivative, 1,3-bis(hydroxyethyl)-5,5-dimethylhydantoin [26850-24-8], is used in the manufacture of high temperature polyesters, polyurethanes, and coatings, offering improved heat resistance, uv stability, flexibility, and adhesion.

1-Hydroxymethyl-5,5-dimethylhydantoin [116-25-6] is used as an odorless donor of formaldehyde for adhesive applications. Under other reaction conditions 5,5-dimethylhydantoin—formaldehyde resins are obtained, which are described in the patent literature as useful additives for several purposes.

8.3. Epoxy Resins

Urethane and ester-extended hydantoin epoxy resins cured with several compounds seem to have better properties than the previous ones (98). These resins are prepared from hydantoins such as (**21**) (99, 100).



(**21**)

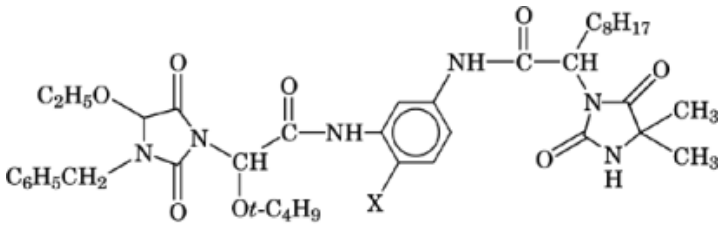
Adding amines to coating compounds containing other polymers of hydantoin derivatives permits thermal curing of the coating compounds, which are useful as electrical insulators of wires under a broad range of conditions without loss of coating flexibility (101).

8.4. 5-Substituted Hydantoins

5-Methylhydantoin [616-03-5] has been selected from several structures as a formaldehyde scavenger for color photosensitive materials and water-thinned inks and coatings (102, 103).

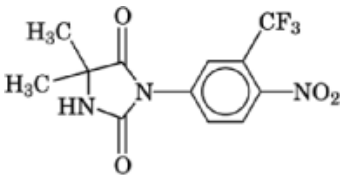
8.4.1. 5,5-Dimethylhydantoins

Some 5,5-dimethylhydantoin derivatives such as (**22**) have been patented as color photographic couplers (104):

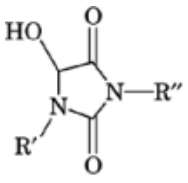


(**22**)

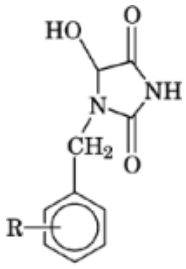
Although the hydantoin ring itself does not present any medicinal activity, many 5,5-disubstituted hydantoins have shown interesting biological properties, and some of them are used in medicine. 5,5-Dimethyl-3-[4-nitro-3-(trifluoromethyl)phenyl]hydantoin [63612-50-0] (**23**) (105) is a pure antiandrogen that inhibits the testicular steroidogenic pathway, apparently acting by forming complexes with the cytoplasmic hormone receptors that are unable to undergo translocation into nuclei, thus blocking most of the biological response of the target cell to androgens (106). It has been proposed for a combined treatment with a potent LHRH agonist to block androgen formation, as the hormonal therapy of choice in prostatic carcinoma (107).



(**23**)



(**24**)



(25)

8.4.2. 5-Hydroxyhydantoins

Some 5-hydroxyhydantoins such as (**24**) and (**25**) have shown antidiabetic activity (108). In some cases they are also diuretics and hypolipemics. These properties are probably related to the urea moiety found in these compounds.

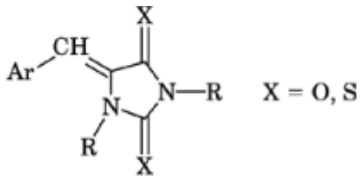
8.4.3. 5-Phenylhydantoins

In spite of the different examples of biological actions, 5,5-disubstituted hydantoins are mainly considered as anticonvulsant agents (109), the most notable being 5,5-diphenylhydantoin (Dilantin, Phenytoin). This compound was introduced in 1938 (110), and despite significant toxic and teratological effects, is still a broadly used anticonvulsant for treatment of epilepsy. The mechanisms of the anticonvulsant action in this and related compounds have been well studied (111, 112). A general model comprising two aromatic rings or their equivalents in a favored orientation, and a third region, usually a cyclic ureide, with a number of H-bond-forming groups has been proposed as pharmacophore (113). Its antiarrhythmic activity (114) as well as its plasma protein binding and metabolism, are relevant (115, 116). In this context, tracers for phenytoin suitable for its determination in body fluids have been prepared by using *p*-aminophenytoin bound to carboxyfluorescein (117, 118).

Another anticonvulsant, formerly used as a hypnotic, is 5-ethyl-5-phenylhydantoin [631-07-2] (Nirvanol, Mephenytoin). Its *S* isomer is stereo-selectively eliminated in most subjects, a fact having clinical consequences with both desired and untoward effects (119).

8.4.4. 5-Arylmethylenehydantoins

5-Arylmethylenehydantoins such as (**26**) are cyclooxygenase and 5-lipoxygenase inhibitors and have been patented as antiinflammatory and antiallergy agents (120).

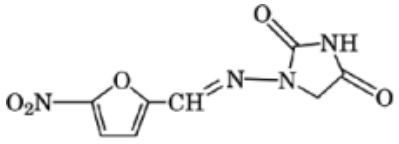


(26)

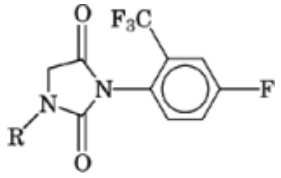
8.5. Other Derivatives

Among the different pharmacological activities described, the 5-nitro-2-furyl-methylimino derivatives such as nitrofurantoin [67-20-9] (**27**) show antimicrobial activity and have been specially proposed for urinary tract

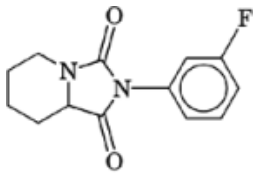
infections, but they may induce DNA damage and cytotoxicity (121, 122). Some 3-arylhydantoins such as (**28**) are effective schistosomicides (123). Many others have been proposed as antifungals, insecticides, nematocides, and soil pesticides. Several types of hydantoin derivatives behave as herbicides, and a study of quantitative structure—activity relationships has been published (123) for compounds related to [60725-62-4] (**29**). Polyhalomethylsulfenylhydantoins exhibit fungicidal activity (124, 125). Thus 1,3-bis(trihalomethylsulfenyl)- (**30**) and 3-aryl-1-[(1,1,2,2-tetrachloroethyl)thio]hydantoins (**31**), protect vines against *Plasmopara viticola*. Organophosphorous derivatives (phosphono- or phosphorothiolates) are useful as pesticides (126). As herbicides, hydantoins are included in the uracil group (127).



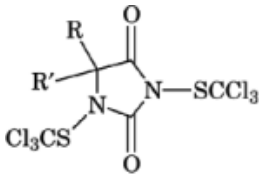
(**27**)



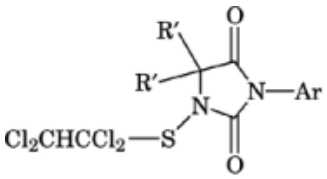
(**28**)



(**29**)

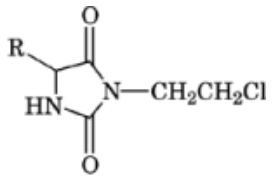


(**30**)

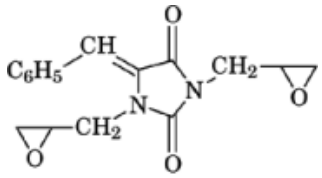


(**31**)

Some hydantoins are very useful carriers of the nitrogen mustard moiety bis (β-chloroethyl)amine, and are useful in several tumors and multiagent therapy regimens (128, 129). Besides that, some 3-(2-chloro-ethyl)hydantoins (**32**) (130) and oxyranylmethylhydantoins, eg, 5-benzylidene-1,3-bis(oxyranylmethyl)hydantoin [79413-02-8] (**33**) (131), among other *N*-glycidylated oxo—nitrogen heterocycles, have shown antitumor activity.

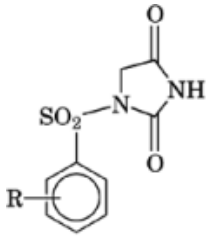


(**32**)

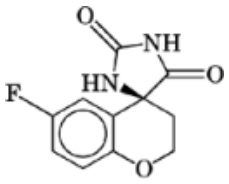


(**33**)

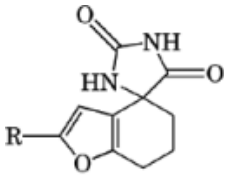
The 1-arylsulfonylhydantoins (**34**), especially 1-[(4-methylsulphenyl)]- and 1(4-bromophenyl)sulfonylhydantoins (132, 133) and several 5,5-spirohydantoins, including sorbinil [68367-52-2] (**35**) and structures (**36**) and (**37**), are inhibitors of aldose reductase, and may be useful in the treatment of chronic diabetic complications such as cataract, because this disease results from the accumulation of polyols derived from sugars in the presence of aldose reductase (134). A computer-automated structure evaluation program has been used to study many relevant compounds and generate activating—inactivating fragments (135).



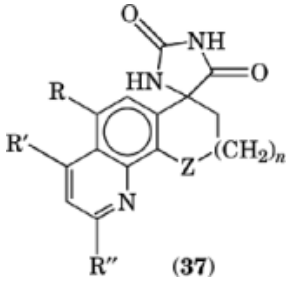
(**34**)



(**35**)

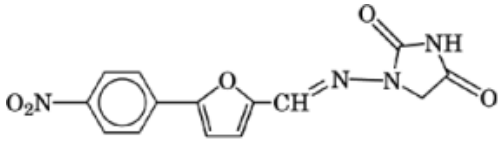


(36)

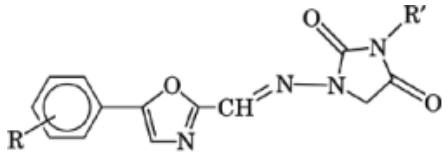


(37)

Structurally related to nitrofurantoins are Dantrolene [7261-97-4] (**38**), a peripherally acting muscle relaxant, and its analogues (**39**), which can be used as an antidote against succinylcholine-induced myopathy and in autoimmune myasthenia gravis therapy (136, 137).



(38)



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BIBLIOGRAPHY

"Hydantoin" in *ECT* 2nd ed., Vol. 2, pp. 141–164, by E. Smith, Olin Mathieson Chemical Corp.; "Hydantoin and Derivatives" in *ECT* 3rd ed., pp. 692–711, by J. H. Bateman, CIBA-GEIGY Corp.

Cited Publications

1. G. R. Pettit and co-workers, *Can. J. Chem.* **68**, 1621 (1990).
2. E. Ware, *Chem. Rev.* **46**, 403 (1950).
3. E. S. Schipper and A. R. Day, in R. C. Elderfield, ed., *Heterocyclic Compounds*, Vol. **5**, John Wiley & Sons, Inc., New York, 1957, p. 254.

4. C. Avendaño and G. G. Trigo, *Adv. Heterocycl. Chem.* **38**, 177 (1985).
5. S. A. Avetisyan, L. V. Azaryan, and S. L. Kockarov, *Arm. Khim. Zh.* **39**, 151 (1986) and **41**, 548 (1988).
6. J. T. Edward, *Chem. Org. Sulf. Comp.* **2**, 287 (1966).
7. R. E. Stuckey, *J. Chem. Soc.*, 5075 (1957).
8. M. J. Bausch, B. David, P. Dobrowolski, and V. J. Prassad, *J. Org. Chem.* **55**, 5806 (1990).
9. L. S. Rosenberg and J. L. Jackson, *Drug Der. Ind. Pharm.* **15**, 373 (1989).
10. H. Fujioka and T. Tan, *J. Pharm. Dyn.* **5**, 475 (1982).
11. S.-F. Tan, K.-P. Ang, Y.-F. Fong, and H. Jayachandran, *J. Chem. Soc. Perkin Trans. II*, 473 (1988).
12. M. J. Bausch and co-workers, *J. Org. Chem.* **56**, 5643 (1991).
13. E. Santos, I. Rosillo, B. del Castillo, and C. Avendaño, *J. Chem. Res., Synop.*, 131 (1982).
14. S. P. Agarwal and M. I. Blake, *J. Pharm. Sci.* **57**, 1434 (1968).
15. H. C. Carrington and W. S. Waring, *J. Chem. Soc.*, 354 (1950).
16. J. T. Edward and J. K. Liu, *Can. J. Chem.* **50**, 2423 (1972).
17. A. R. Katritzky and P. J. Taylor in A. R. Katritzky, ed., *Physical Methods in Heterocyclic Chemistry*, Vol. **4**, Academic Press, New York, 1971, p. 265.
18. J. Bellanato, C. Avendaño, P. Ballesteros, and M. Martínez, *Spectrochim. Acta* **35A**, 807 (1979).
19. J. Derkosh, *Monatsch. Chem.* **92**, 361 (1961).
20. J. Bellanato, C. Avendaño, P. Ballesteros, E. Santos, and G. G. Trigo, *Spectrochim. Acta* **36A**, 879 (1980).
21. M. Willson, T. Boissou, R. Mathis, and F. Mathis, *Spectrochim. Acta* **40A**, 835 (1984).
22. R. A. Corral and O. O. Orazi, *Spectrochim. Acta* **21**, 2119 (1965).
23. S.-F. Tan, K.-P. Ang, H. Jayachandran, and Y.-F. Fong, *J. Chem. Soc. Perkin Trans. II*, 1043 (1987).
24. C. Pedregal, M. Espada, J. Albert, E. Cruz, and A. Virgili, *Magn. Res. Chem.* **29**, 1226 (1991).
25. M. Bausch, D. Selmarten, R. Gostowski, and P. Dobrowolski, *J. Phys. Org. Chem.* **4**, 67 (1991).
26. F. Cristiani, F. A. Devillanova, A. Díaz, F. Isaia, and G. Verani, *Spectrosc. Lett.* **21**, 767 (1988).
27. M. S. Fadeeva, R. S. Lebedev, T. I. Filaeva, and O. Y. Sdonova *Deposited Doc.*, VINITI 4969 (1982).
28. R. A. Corral, O. O. Orazi, A. M. Duffield, and C. Djerassi, *Org. Mass Spectrom.* **5**, 551 (1971).
29. R. A. Locock and R. T. Coutts, *Org. Mass Spectrom.* **3**, 735 (1972).
30. G. Ruecker, P. N. Natarajan, and A. F. Fell, *Arch. Pharm.* **304**, 833 (1971).
31. R. E. Ardrey and A. Darbre, *J. Chromatogr.* **87**, 499 (1973).
32. T. Sizuki, K. S. Song, and K. Tuzimura, *Org. Mass Spectrom.* **11**, 557 (1976).
33. B. M. Kown and S. Ch. Kim, *J. Chem. Soc. Perkin Trans. II*, 761 (1983).
34. H. M. Fales, Y. Nagai, G. W. A. Milne, H. B. Brewer, T. Brouzert, and J. J. Pisano, *Anal. Biochem.* **43**, 288 (1971).
35. O. O. Orazi, R. A. Corral, and H. Schuttenberg, *J. Chem. Soc. Perkin Trans. II*, 219 (1974).
36. O. O. Orazi and R. A. Corral, *Experientia* **21**, 508 (1965).
37. P. López-Alvarado, C. Avendaño, and J. C. Menéndez, *Tetrahedron Lett.* **33**, 6875 (1992).
38. O. O. Orazi and R. A. Corral, *Tetrahedron* **15**, 93 (1961).
39. J. W. Shaffer, R. Scheasley, and M. B. Winstead, *J. Med. Chem.* **10**, 739 (1967).
40. J. W. Shaffer, E. Steinberg, V. Krimsley, and M. B. Winstead, *J. Med. Chem.* **11**, 462 (1968).
41. S. Suri and R. D. Chapman, *Synthesis*, 743 (1988).
42. G. G. Trigo, C. Avendaño, E. Santos, J. T. Edward, and S. C. Wong, *Can. J. Chem.* **57**, 1456 (1979).
43. J. C. Menéndez and M. M. Söllhuber, *Heterocycles* **26**, 3203 (1987).
44. T. Moriya, K. Hagio, and H. Yoneda, *Chem. Pharm. Bull.* **28**, 1891 (1980).
45. S. Nagase, *Nippon Kagaku Zasshi* **81**, 938 (1960).
46. H. A. F. Daboun, S. E. Abdou, M. M. Hussein, and M. H. Elnagdi, *Synthesis*, 502 (1982).
47. S. Takahashi, *Kikan Kagaku Sosetu*, 111 (1989).
48. E. M. Meijer, W. H. J. Boesten, H. E. Schaemaker, and J. A. M. Van Balken, in J. Tramper, H. C. van der Plas, and P. Linko, eds., *Biocatalysis in Organic Synthesis*, Elsevier, Amsterdam, 1985, p. 135.
49. I. J. Wilk and W. Close, *J. Org. Chem.* **15**, 1020 (1950).
50. J. Cortes and H. Kohn, *J. Org. Chem.* **48**, 2247 (1983).
51. F. J. Marshall, *J. Am. Chem. Soc.* **78**, 3696 (1956).
52. E. de la Cuesta, P. Ballesteros, and G. G. Trigo, *Heterocycles* **16**, 1647 (1981).
53. J. Rubido, C. Pedregal, M. Espada, and J. Elguero, *Synthesis*, 307 (1985).

54. H. R. Divanfard, Y. A. Ibrahim, and M. M. Joullié, *J. Heterocycl. Chem.* **15**, 691 (1978).
55. J. C. Gramain and R. Remuson, *J. Chem. Soc. Perkin Trans. I*, 2341 (1982).
56. J. C. Gramain, J. P. Jendrau, J. Lemaire, and R. Remuson, *Rec. Trav. Chim. Pays-Bas* **109**, 325 (1990).
57. H. E. Zangg and W. B. Martin, *Org. React.* **14**, 60 (1965).
58. D. Ben-Ishai and E. Goldstein, *Tetrahedron* **27**, 3119 (1971).
59. S. M. Weinreb and co-workers, *J. Am. Chem. Soc.* **104**, 536 (1982).
60. W. T. Read, *J. Am. Chem. Soc.* **44**, 1766 (1922).
61. J. C. Menéndez, M. P. Díaz, C. Bellver, and M. Söllhuber, *Eur. J. Med. Chem.* **27**, 61 (1992).
62. R. Sarges, H. R. Howard, and P. R. Kelbaugh, *J. Org. Chem.* **47**, 4081 (1982).
63. I. Ugi, *Angew. Chem.* **74**, 9 (1962).
64. M. Espada and co-workers, *Il Farmaco (Sci. Ed.)* **45**, 1237 (1990).
65. J. C. Menéndez and M. M. Söllhuber, *J. Heterocycl. Chem.* **28**, 923 (1991).
66. J. Knabe and W. Wutton, *Arch. Pharm.* **313**, 538 (1980).
67. S. Icli and L. D. Colebrock, *J. Pure Appl. Sci.* **9**, 39 (1976).
68. T. Ohashi, S. Takahashi, T. Nagamachi, K. Yoneda, and H. Yamada, *Agric. Biol. Chem.* **45**, 831 (1981).
69. J. T. Edward and C. Jitransgri, *Can. J. Chem.* **53**, 3339 (1975).
70. G. G. Trigo, C. Avendaño, E. Santos, J. T. Edward, and S. C. Wong, *Can. J. Chem.* **57**, 1456 (1979).
71. H. C. Carrington, *J. Chem. Soc.*, 681 (1947).
72. H. C. Carrington, C. H. Vasey, and W. S. Warings, *J. Chem. Soc.*, 396 (1959).
73. P. Macheras and A. Rosen, *Pharmazie* **39**, 322 (1984).
74. P. Messinger and H. Mayer, *Pharm. Ztg.* **122**, 2253 (1977).
75. G. Stajer, *Arch. Pharm.* **310**, 865 (1977).
76. H. Stamm, *Dtsch. Apoth. Ztg.* **110**, 1206 (1970).
77. W. Wiegrebe and L. Wehrhahn, *Arzneim-Forsch.* **25**, 517 (1975).
78. H. J. Roth, K. Eger, and R. Troschütz, *Pharmaceutical Chemistry*, Vol. **2**, Ellis Horwood, Chichester, U.K., 1991, p. 302.
79. J. Philip, I. J. Holcomb, and S. A. Fusari, in K. Florey, ed., *Analytical Profiles of Drug Substances*, Vol. **13**, Academic Press, Orlando, Fla., 1984, p. 417.
80. Y. Ishikawa, T. Kumazawana and T. Takahashi, *Z. Rechtsmed.* **99**, 253 (1988).
81. I. Junko and S. Takahashi, *Bunseki Kagaku* **38**, 659 (1989).
82. G. Jaouen, A. A. Ismail, and P. Brossier, PCI Int. Appl. WO 88 07, 684 (Oct. 6, 1988).
83. G. L. Jones, G. H. Wimbish, and W. E. McIntosh, *Med. Res. Rev.* **3**, 383 (1983).
84. H. Tatsumoto, R. Nakagawa, and S. Suzuki, *Kankyo Kagaku Kenkyu Hokoku (Chiba Daigaku)* **9**, 51 (1984).
85. R. A. Corral and O. O. Orazi, *J. Org. Chem.* **28**, 1100 (1963).
86. A. R. Suárez and O. A. Orio, *An. Asoc. Quím. Argent.* **65**, 163 (1977).
87. Ch. H. Cook, S. S. Jew, and Y. S. Chung, *Arch. Pharmacol. Res.* **5**, 103 (1982).
88. M. Rizk, M. I. Walash, A. A. Obou-Ouf, and F. Beeal, *Anal. Lett.* **14**, 1407 (1981).
89. I. Rizk, A. A. Obou-Ouf, and F. Belal, *Anal. Lett.* **16(A2)**, 129 (1983).
90. M. I. Walash, M. I. Rizk, A. M. Obou-Ouf, and F. Beeal, *Analyst* **108**, 626 (1983).
91. M. P. Radhamoma and P. Indrasenan, *Talanta* **30**, 49 (1983).
92. M. J. Blais, O. Enea, and G. Berthon, *Termochim. Acta* **30**, 45 (1979).
93. F. Barragán, M. T. Montaña, and J. L. Gómez-Ariza, *Microchem. J.* **25**, 524 (1980).
94. M. T. Montaña, and J. L. Gómez-Ariza, *Microchem. J.* **25**, 360 (1980).
95. U. S. Pat. 4,297,224 (Oct. 27, 1981), N. T. Machiarolo, B. McGuire, and J. M. Scalise (to Great Lakes Chemical Corp.).
96. Eur. J. Pat. Appl. EP 176,163 (Apr. 2, 1986), R. A. Robinson, W. J. Boan, and G. D. Evans (to Purex Corp.).
97. S. D. Worley, W. B. Wheatley, and H. H. Kohl, *Ind. Eng. Chem. Prod. Res. Der.* **22**, 716 (1983).
98. J. Weiss, *Sci. Tech. Aerosp. Rep.* **21**, N83-22323 (1983).
99. D. Porret, *Makromol. Chem.* **108**, 73 (1967).
100. E. H. Catsiff, R. E. Coulehan, J. F. DiPrima, D. A. Gordon, and R. Seltzer, *Org. Coat. Plast. Chem.* **39**, 139 (1978).
101. Ger. Offen, DE 3,242,162 (May 17, 1984). K. Sirinyan, F. Jonas, and R. Merten (to Bayer A. G.).
102. Jpn. Kokai Tokkyo Koho JP 58,153,934 (Sept. 13, 1983), (to Konishiroku Photo Industry Co., Ltd.).
103. Jpn. Kokai Tokkyo Koho JP 58,198,570 (Nov. 18, 1983), (to Dainippon Ink and Chemicals Inc.).

104. Jpn. Kokai Tokkyo Koho JP 60,249,150 (Dec. 9, 1985), A. Ogawa, M. Tsuda, and K. Nakajo (to Fuji Photo Film Co., Ltd.).
105. T. Ojasoo and J. P. Raynaud, *Prog. Cancer Res. Ther.* **25**, 11 (1983).
106. J. G. Tezon, M. H. Vázquez, and J. A. Blaquier, *Endocrinology* **111**, 2039 (1982).
107. F. A. Lefebvre, C. Seguin, A. Belanger, S. Caron, M. R. Sariam, and F. Labrie, *Prostate* **3**, 569 (1982).
108. Jpn. Kokai Tokkyo Koho JP 60,188,373 (Sept. 25, 1985), (to Nippon Zoki Pharmaceutical Co., Ltd.).
109. A. Spinks and W. S. Waring, *Progr. Med. Chem.* **3**, 313 (1963).
110. H. H. Merrit and T. J. Putman, *J. Am. Med. Assoc.* **111**, 1068 (1938).
111. W. E. Stone and M. J. Javid, *Neurol. Res.* **7**, 202 (1985).
112. Y. Yaari, M. E. Selzer, and J. H. Pincus, *Ann. Neurol.* **20**, 171 (1986).
113. M. G. Wong, J. A. Defina, and P. R. Andrews, *J. Med. Chem.* **29**, 562 (1986).
114. W. Spinelly and M. R. Roseu, *J. Pharmacol. Exp. Ther.* **238**, 794 (1986).
115. E. Perucca, *Ther. Drug Monit.* **2**, 331 (1980).
116. D. Kadar, T. D. Fecycz, and W. Kalow, *J. Physiol. Pharmacol.* **61**, 403 (1983).
117. Ger. Offen. DE 3,205,506 (Sept. 16, 1982), C. H. J. Wang, S. D. Stroupe, and M. E. Jolley (to Abbott Laboratories).
118. K. Tasaka, R. Terao, Ch. Kamei, K. Hashigaki, and M. Yamato, *Int. J. Immunopharmacol.* **9**, 391 (1987).
119. W. S. Aslanian, E. Jacqz, C. B. McAllister, R. A. Branch, and G. R. Wilkinson, *J. Pharmacol. Exp. Ther.* **234**, 662 (1985).
120. Eur. Pat. Appl. EP 343,643 (Nov. 29, 1989), W. A. Cetenko, D. T. Connor, R. J. Sorenson, P. C. Unangst, and S. R. Stabler (to Warner-Lambert Co.).
121. N. E. McCarroll, B. H. Keech, and C. E. Piper, *Environ. Mutagen.* **3**, 607 (1981).
122. M. Korbelik, *Arch. Hig. Rada Toksikol.* **31**, 227 (1980).
123. H. Ohta, T. Jikihara, K. Wakabayashi, and T. Fujita, *Pestic. Biochem. Physiol.* **14**, 153 (1980).
124. U.S. Pat. 4,198,423 (Apr. 15, 1980), C. J. Mappes, E.-H Pommer, and B. Zeeh (to BASF A. G.).
125. Belg. Pat. 631,731 (May 2, 1962), E. Klauke, E. Kuehle, and F. Graven (to Bayer A.G.).
126. Eur. Pat. Appl. EP 186,124 (July 2, 1986), T. Haga, T. Koyanagi, K. Yoshida, O. Imai, and H. Okada (to Ishihara Sangyo Kaisha, Ltd.).
127. S. Saltzman, A. J. Acher, N. Brates, M. Horowitz, and A. Gevelberg, *Pestic. Sci.* **13**, 211 (1982).
128. G. Peng, V. Márquez, and J. S. Driscoll, *J. Med. Chem.* **18**, 846 (1975).
129. F. D. Deen, T. Hoshino, M. E. Williams, K. Nomura, and P. M. Bartle, *Cancer Res.* **39**, 4336 (1979).
130. J. C. Kim and co-workers, *Yakhak Hoechi* **27**, 309 (1983).
131. H. Fischer, H. Moeller, M. Budnowski, G. Atassi, P. Dumont, J. Venditti, and O. C. Yoder, *Arzneim.-Forsch.* **34**, 663 (1984).
132. Jpn. Kokai Tokkyo Koho JP 58,109,418 (June 29, 1983), H. Okuda.
133. K. Inagaki, I. Miwa, T. Yashiro, and J. Okuda, *Chem. Pharm. Bull.* **30**, 3244 (1982).
134. L. G. Humber, *Progr. Med. Chem.* **24**, 299 (1987).
135. G. Klopman and E. Buyukbingol, *Mol. Pharmacol.* **34**, 852 (1988).
136. M. Endo and S. Yagi, *Electroencephalogr. Clin. Neurophysiol. Suppl.* **36**, 261 (1982).
137. R. L. White, F. L. Wessels, T. J. Schwan, and K. O. Ellis, *J. Med. Chem.* **30**, 263 (1987).

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