Attempted Catalytic Decomposition of the Potassium and Silver Salts of 4-Hydroxy-2′,6′-diiodo-4′-chlorodiphenyl Ether.—The potassium and silver salts of 4-hydroxy-2′,6′-diiodo-4′-chlorodiphenyl ether were prepared by the usual methods. They were subjected to the action of the above catalysts under similar conditions, but in no case did a decomposition to amorphous oxide occur.

Summary

1. 4-Hydroxy-3,5-dibromo-2′,6′-diiodo-4′-chlorodiphenyl ether, a new halogenated phenol related to the symmetrically trihalogenated phenols, has been prepared.

2. The catalytic decomposition of metallic salts of the new phenol has been studied. The decomposition occurs in a manner entirely analogous to that of the trihalogenated phenols previously studied. It was observed that only the halogen in the hydroxyl-bearing nucleus is removed in such decomposition.

3. Additional confirmation of the mechanism previously suggested for the catalytic decomposition of metal salts of halogenated phenols has been obtained.

4. Additional evidence for the existence of Type A and Type B radicals has been disclosed.

MINNEAPOLIS, MINNESOTA
WILMINGTON, DELAWARE

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, YALE UNIVERSITY]

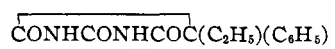
RESEARCHES ON HYDANTOINS. L.[1] THE SYNTHESIS OF HYDANTOINS POSSESSING THE PROPERTIES OF HYPNOTICS

BY ROBERT M. HERBST[2] AND TREAT B. JOHNSON

RECEIVED JANUARY 29, 1932 PUBLISHED JUNE 6, 1932

That the hydantoin nucleus exhibits hypnotic properties has been known for several years. This pharmacological behavior is most pronounced in the drug *"nirvanol"* (phenylethylhydantoin) I, which is the hydantoin analog of the pyrimidine *"luminal"* or phenylethylbarbituric acid II. The latter cyclic ureide and several of its representatives have been used effectively as sedatives and hypnotics in simple insomnia, hysteria, neurasthenia, thyroid disease, chorea, epilepsy and certain mental disturbances.

I



II

Although nirvanol I has fallen into disrepute in recent years as an hypnotic because of the fever and skin eruptions induced by its continued ad-

[1] Constructed from a dissertation presented by Robert M. Herbst to the Faculty of the Graduate School of Yale University in partial fulfilment of the requirements for the degree of Doctor of Philosophy, June, 1930.

[2] Eli Lilly Company Graduate Scholar, 1928–1929.

ministration, it has recently been found to exert a valuable therapeutic action on certain nervous disorders. Several physicians working in hospitals have reported to this Laboratory remarkable successes in the clinical treatment of chorea (St. Vitus' dance) with this hydantoin I.[3] However, here too the drug must be administered continuously over a period of time, and the undesirable reactions are also manifested. Peculiarly, the disappearance of the characteristic skin eruptions and fever induced by nirvanol is coincident with the disappearance of the symptoms of chorea. The work discussed in this paper represents a part of a co-operative research program, organized for the purpose of synthesizing a group of new hydantoin derivatives which might be better suited than *nirvanol* to the treatment of chorea and other nervous disorders. Very little attention has thus far been paid to the pharmacology of this class of organic compounds.

For the preparation of dialkyl-hydantoins we have employed a method first applied by Urech[4] and recently studied by Read[5] of this Laboratory, and also by Biltz and Slotta,[6] whereby the desired hydantoins may be prepared from ketones in three steps as is expressed by the formulas

$$RCOR' + NH_4CN \longrightarrow RR'C(NH_2)CN \longrightarrow$$

$$RR'C(NHCONH_2)CN \longrightarrow HN{=}\overline{C\text{NHCONHC}}RR' \longrightarrow CONHCONHCRR'$$

IV V VI

In the third step of this process (IV ⟶ VI) we postulate that the reaction takes place through the formation of an intermediate imino-hydantoin V, which in strongly acid solution is immediately decomposed, giving the corresponding dialkyl-hydantoin VI. The conversion of the hydantoin nitrile IV to the hydantoin VI in hot acid solution proceeds with such rapidity that the reaction is practically instantaneous. This suggests that another reaction mechanism than that involved in the normal hydrolysis of a cyanide group, which is usually a slower reaction, is to be considered. In a previous paper[7] the authors have described a rearrangement of an hydantoic-nitrile IV, to a stable 4-aminohydantoin, a molecular change which, we believe, lends support to the mechanism of reaction suggested above.

[3] Private communication from Dr. S. W. Clausen of the Strong Memorial Hospital, University of Rochester, Rochester, New York. Also the drug has been used with success in the clinics of several medical schools, including Yale, during the past two years. See also "Phenylethylhydantoin in the Treatment of Syndenham's Chorea" by Ray and Cunningham, *Am. J. Diseases of Children*, **39**, 1205 (1930).

[4] Urech, *Ann.*, **164**, 255 (1872).

[5] See Read, THIS JOURNAL, **44**, 1746 (1922), for a review of the literature on methods of synthesis.

[6] Biltz and Slotta, *J. prakt. Chem.*, **113**, 233 (1926).

[7] Herbst and Johnson, THIS JOURNAL, **52**, 3676 (1930).

Experimental Part

Preparation of Ketones.—Several of the ketones employed in the synthesis of alkylated hydantoins were prepared by the catalytic method of Senderens,[8] in which thorium oxide carried on pumice served as the catalyst. Methyl benzyl ketone was prepared by passing the vapors of a mixture of acetic acid and phenylacetic acid over the catalyst at a temperature of 430–450°. Similarly ethyl benzyl ketone and ethyl β-phenylethyl ketone were prepared catalytically by heating mixtures of propionic acid with phenylacetic and hydrocinnamic acids, respectively. Varying amounts of the two possible symmetrical ketones are always formed as by-products and may be recovered. Benzylacetone was prepared for our research by reducing benzalacetone[9] with hydrogen gas at a pressure of 2 to 3 atmospheres in the presence of Adams' platinum oxide catalyst.[10]

The Preparation of Nitriles of Amino Acids from Ketones.—The amino acid nitriles corresponding to the ketones were prepared by the action of anhydrous hydrocyanic acid and ammonia on a solution of the respective ketone in absolute ethyl alcohol. These compounds are usually isolated most conveniently in the form of their hydrochlorides. The technique employed was as follows.

A solution of 0.25 mole of the ketone in 25 cc. of absolute ethyl alcohol is thoroughly cooled with ice water; 0.25 mole of anhydrous hydrocyanic acid is added, followed by 0.25 mole of anhydrous ammonia. During the addition of the ammonia the flask in which the reaction is applied is thoroughly cooled, and equipped with a good reflux condenser to prevent loss of hydrocyanic acid, since considerable heat is evolved in the formation of ammonium cyanide. This procedure is much more convenient than that previously recommended by Read[5] in which solid ammonium cyanide is first prepared for the reaction with the ketone.

The solution containing the ketone and ammonium cyanide is transferred to a pressure bottle, and the mixture allowed to stand from twenty-four to seventy-two hours until the reaction is complete, or equilibrium is established. The contents are then poured into a mixture of 200 g. of cracked ice and 50 cc. of concentrated hydrochloric acid. Any unreacted ketone separates as an oil, and may be removed by extraction with ether. The desired amino-nitrile is liberated by the addition of a slight excess of concentrated ammonia, keeping the solution well cooled by the addition of cracked ice. It separates as an oil which takes up in the ether and is separated from the aqueous layer, which is further extracted twice with fresh ether. The ether solutions are combined and dried over sodium sulfate. The hydrochloride of the amino-nitrile is precipitated from the ether solution by the addition of dry hydrogen chloride.

The hydrochloride of α-amino-α-methyl-γ-phenylbutyronitrile, from benzylacetone, precipitates practically completely from the acid water solution and the steps involving liberation of the aminonitrile and subsequent precipitation from ether solution are omitted in this case. The hydrochloride of 1-amino-1-cyanocyclohexane precipitates partially from the acid water solution. The remainder is obtained in the manner described above. The hydrochloride of α-amino-α-ethyl-γ-phenylbutyronitrile is not precipitated readily as a solid from ether solution with dry hydrogen chloride; consequently it was used as the free base, which was obtained by evaporating the ether from the dry solution of the amino-nitrile under reduced pressure at room temperature. A small amount of the hydrochloride was prepared by dissolving the amino-nitrile in dilute aqueous hydrochloric acid, and saturating the cold solution with hydrogen chloride,

[8] Senderens, *Ann. chim. phys.*, [8] **28**, 318 (1913).

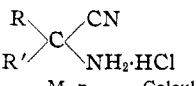
[9] Vavon, *Compt. rend.*, **154**, 1706 (1912).

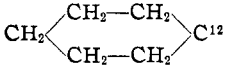
[10] Adams and Shriner, THIS JOURNAL, **45**, 2171 (1923)

whereupon the hydrochloride of α-amino-α-ethyl-γ-phenylbutyronitrile precipitated in the form of colorless needles.

The new amino acid nitriles prepared in this research are recorded in Table I.

TABLE I



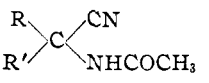
R	R′	Formula	M. p., °C. (corr.)	Calculated, % N	Cl	Found, % N	Cl	Yield,[a] %
CH_3	$CH_2C_6H_5$	$C_{10}H_{13}N_2Cl$	148–150	14.25	...	14.17 14.21	...	86.5
C_2H_5	$CH_2C_6H_5$[11]	$C_{11}H_{15}N_2Cl$	135–140	13.30	16.84	13.30 13.23	17.05	81
CH_3	$CH_2CH_2C_6H_5$	$C_{11}H_{15}N_2Cl$	140–141	13.30	...	13.28	...	88
C_2H_5	$CH_2CH_2C_6H_5$	$C_{12}H_{17}N_2Cl$	84	11.45	...	11.73	...	85
		$C_7H_{13}N_2Cl$	202–204	17.45	22.08	17.42 17.20	22.35	77

[a] The yields are calculated allowing for recovered ketone, which never amounted to more than 25–30% of the original material.

The amino acid nitrile hydrochlorides are all soluble in water, somewhat soluble in 95% ethyl alcohol, and insoluble in most other organic solvents. The hydrochlorides of α-amino-α-methyl-γ-phenylbutyronitrile and 1-amino-1-cyanocyclohexane are stable; the rest decompose slowly on standing. Also the free nitriles are oils in the crude state, very slightly soluble in water, and somewhat unstable, especially toward heat. Since it was impossible to distil them under reduced pressure, purification was not attempted.

The acetylamino-nitriles were prepared by treating the free amino acid nitriles with acetic anhydride in the usual manner. The new compounds prepared are given in Table II.

TABLE II



R	R′	Formula	M. p., °C.	N Analyses, % Calcd.	Found	
CH_3	$CH_2C_6H_5$	$C_{12}H_{14}ON_2$[a]	142–143	13.86	13.78	13.81
C_2H_5	$CH_2C_6H_5$	$C_{13}H_{16}ON_2$[b]	86– 87	12.96	12.97	
C_2H_5	$CH_2CH_2C_6H_5$	$C_{14}H_{18}ON_2$[c]	116–118	12.17	12.29	

[a] Small colorless needles from toluene. [b] Colorless needles from benzene containing benzene of crystallization. [c] Colorless needles from water.

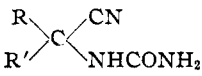
The Ureido-nitriles.—The method used by Read[5] for the preparation of ureido-nitriles from amino acid nitrile hydrochlorides was employed with slight modification in technique. The amino acid nitrile hydrochloride, suspended or dissolved in a suitable medium, is treated carefully with two equivalents of potassium cyanate. Read employed glacial acetic acid as a solvent for this reaction. We have also used this medium, but have found 50% acetic acid better suited in several cases. Moreover, we have found it necessary to neutralize the acetic acid with ammonia in order to obtain complete precipitation of the ureido-nitriles after the reaction mixture is diluted with water accord-

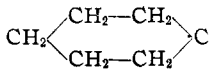
[11] Jawelow, *Ber.*, **39**, 1199 (1906).

[12] Smessarew, *J. prakt. Chem.*, **89**, 369 (1914).

ing to Read's procedure. The new ureido-nitriles prepared by us are recorded in Table III.

TABLE III

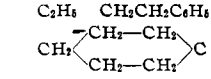


R	R′	Formula	M. p., °C.	N Analyses, % Calcd.	Found	Yield, %
CH_3	$CH_2C_6H_5$[a]	$C_{11}H_{13}ON_3$	170–171	20.59	20.47	86
C_2H_5	$CH_2C_6H_5$[b]	$C_{12}H_{15}ON_3$	124–126	19.35	19.22	91
CH_3	$CH_2CH_2C_6H_5$[a]	$C_{12}H_{15}ON_3$	138–142	19.35	19.38	83
C_2H_5	$CH_2CH_2C_6H_5$[b]	$C_{13}H_{17}ON_3$	139	18.18	18.15	93
		$C_8H_{13}ON_3$	180–181	25.14	25.15	92

[a] Glacial acetic acid medium for reaction. [b] 50% (volume) acetic acid medium for reaction.

Hydantoins from the Ureido-nitriles.—The formation of hydantoins from the corresponding ureido-nitriles is brought about by warming the nitriles in 20% hydrochloric acid solution, from which the hydantoins precipitate on forming. These are purified by recrystallization from 50% alcohol, from which they usually separate as colorless needles or prisms. The new hydantoins prepared by us are recorded in Table IV.

TABLE IV

R	R′	Formula	M. p., °C. (corr.)	Analyses, % Calculated C	H	N	Found C	H	N		Yield, %
CH_3	$CH_2C_6H_5$	$C_{11}H_{12}O_2N_2$	227–228	64.67	5.93	13.73	64.51	5.75	13.77	13.87	92
C_2H_5	$CH_2C_6H_5$	$C_{12}H_{14}O_2N_2$	217–218	66.01	6.47	12.84	66.06	6.28	12.87	12.91	72
CH_3	$CH_2CH_2C_6H_5$[a]	$C_{13}H_{14}O_2N_2$	179–180	66.01	6.47	12.84	66.05	6.51	12.92	12.67	82
C_2H_5	$CH_2CH_2C_6H_5$	$C_{13}H_{16}O_2N_2$	198–199	67.20	6.95	12.07	67.41	6.80	11.96	11.97	75
		$C_8H_{12}O_2N_2$	217–218	57.10	7.19	16.67	57.26	7.15	16.59	16.76	77

[a] The ureido-nitrile corresponding to this hydantoin melts under hot aqueous hydrochloric acid, and does not dissolve completely, hence the mixture should be stirred vigorously during heating to ensure complete reaction.

5,5-Cyclopentamethylenehydantoin crystallizes from 50% alcohol with one molecule of water of crystallization, which is lost on heating to 105–110°. The following analysis was made on a sample dried to constant weight at 105–110°.

Anal. Calcd. for $C_8H_{12}O_2N_2 \cdot H_2O$: H_2O, 9.67. Found: H_2O, 9.48.

Salts of the Hydantoins with Metals.—The sodium salts of the above hydantoins are easily prepared by treating a small amount of the hydantoin with the calculated quantity of a 5% solution of sodium hydroxide in 95% alcohol. On evaporating the alcohol in a vacuum desiccator, the sodium salt of the hydantoin remains as a colorless, crystalline residue. These salts are very soluble in water, slightly soluble in 95% alcohol, and insoluble in most other organic solvents. Acetic or mineral acids, and carbon dioxide precipitate the hydantoins from aqueous solutions of their sodium salts. Aqueous solutions of the sodium salts absorb carbon dioxide from the air with subsequent precipitation of the free hydantoins. However, the sodium salts are quite stable in aqueous solution when carbon dioxide is excluded. A water solution of the sodium

salt of nirvanol[13] was kept for six weeks in a sealed tube at 40–50°, after which the hydantoin was recovered almost quantitatively on addition of carbon dioxide.

The mercury salts of the hydantoins precipitate as flocculent, colorless solids when a saturated solution of mercuric chloride is added to aqueous solutions of the sodium salts of the hydantoins. Similarly crystalline calcium and magnesium salts of the hydantoins precipitate when strong solutions of calcium chloride and magnesium sulfate, respectively, are added to aqueous solutions of the hydantoin sodium salts.

α-Amino-α-phenylbutyric Acid, $C_6H_5C(C_2H_5)(NH_2)COOH$.—This amino acid was obtained by Jawelow[11] from propiophenone through the action of ammonium cyanide, followed by hydrolysis of the amino acid nitrile formed. His description of the compound is limited to the statement that it separates from water in groups of needles. We have prepared this same amino acid by hydrolyzing phenylethylhydantoin with barium hydroxide.

A mixture of 10 g. of the hydantoin, 50 g. of crystallized barium hydroxide, and 100 cc. of water is refluxed for one hundred hours, when the evolution of ammonia will have practically ceased. The excess of barium hydroxide is precipitated as the carbonate by bubbling carbon dioxide into the mixture. After filtering off the barium carbonate and washing with hot water, the combined filtrate and washings are concentrated until the amino acid begins to crystallize from the solution. On cooling, α-amino-α-phenylbutyric acid separates in the form of clusters of needles. The amino acid is purified by dissolving in dilute ammonia water, and concentrating on the steam-bath until crystallization begins. A yield of 79 g. of the amino acid, melting at 275° (corr.) with charring, was obtained.

Anal. Calcd. for $C_{10}H_{13}O_2N$: C, 67.00; H, 7.32; N, 7.82. Found: C, 67.09; H, 7.25; N, 7.50, 7.50.

The compound shows all the characteristic properties of an α-amino acid. It is soluble in hot water and glacial acetic acid, slightly soluble in cold water and insoluble in most other organic solvents.

Hydrochloride.—This is a colorless, crystalline solid, very soluble in water and melting at 271° (corr.) with charring and effervescence.

Anal. Calcd. for $C_{10}H_{14}O_2NCl$: N, 6.50; Cl, 16.47. Found: N, 6.62; Cl, 16.76.

α-Phenylureido-α-phenylbutyric Acid, $C_6H_5C(C_2H_5)(NHCONHC_6H_5)COOH$, crystallizes from 75% alcohol in small, colorless needles, melting at 190–190.5° (corr.) with complete disappearance of all the material.

Anal. Calcd. for $C_{17}H_{18}O_3N_2$: N, 9.40. Found: N, 9.60.

α-Amino-α-methyl-β-phenylpropionic Acid, $C_6H_5CH_2C(CH_3)(NH_2)COOH$.—This amino acid was prepared from 5-methyl-5-benzylhydantoin in the same manner as that described for α-amino-α-phenylbutyric acid. In this case the hydantoin is completely broken down after thirty hours of boiling with barium hydroxide solution. It crystallizes from water in bunches of colorless needles, melting at 293–294° (corr.) with charring.

Anal. Calcd. for $C_{10}H_{13}O_2N$: C, 67.00; H, 7.32; N, 7.82. Found: C, 66.90; H, 7.18; N, 7.76.

This compound has about the same solubility in various solvents as its isomer, α-amino-α-phenylbutyric acid.

The hydrochloride is a colorless crystalline acid, melting at 244–246° (corr.) with charring and gas evolution.

Anal. Calcd. for $C_{10}H_{14}O_2NCl$: N, 6.50; Cl, 16.47. Found: N, 6.44, 6.46; Cl, 16.49.

[13] Prepared according to Read's method, Ref. 5.

α-Phenyl-ureido-α-methyl-β-phenylpropionic Acid, $C_6H_5CH_2C(CH_3)(NHCONH-C_6H_5)COOH$, crystallizes from 50% alcohol in small, colorless prisms, melting at 187° (corr.) with complete disappearance of the material.

Anal. Calcd. for $C_{17}H_{18}O_3N_2$: N, 9.40. Found: N, 9.49.

Pharmacological Report

The results of a preliminary pharmacological examination of the above hydantoins are summarized in Table V, compiled from a report kindly submitted by Mr. C. L. Rose,[14] of the Lilly Research Laboratories, Indianapolis, Indiana. The hypnotic value of the compounds was tested in the usual manner, by intraperitoneal injection of white rats with a definite volume dose of the material to be tested. The doses were measured in milligrams per kilogram of rat weight, and the results read in terms of dosage, as, Minimum Hypnotic Dose (M. H. D.), Maximum Tolerated Dose (M. T. D.), Minimum Lethal Dose (M. L. D.), and the safety factor or Ratio of M. H. D. to M. T. D.

TABLE V

PHARMACOLOGICAL BEHAVIOR

Compound	M. H. D.	M. T. D.	M. L. D.	Ratio
Ethylphenylhydantoin (nirvanol)	165	190	200	1.21
Methylbenzylhydantoin	550	650	700	1.28
Ethylbenzylhydantoin	500	450	500	1.00
Methyl-β-phenylethylhydantoin	250	500	550	2.20
Ethyl-β-phenylethylhydantoin	275	390	400	1.45
Cyclopentamethylenehydantoin	None	150	200	...

Discussion of the Pharmacological Data

5-Methyl-5-β-phenylethylhydantoin stands out as the best hypnotic of the group. It is less than half as toxic as nirvanol, and its effective dose somewhat approaches that of nirvanol, while its margin of safety is nearly twice that of nirvanol. Next best is 5-ethyl-5-β-phenylethylhydantoin, which is only 9% less effective and 27% more toxic than its methyl analog.

Although 5-methyl-5-benzylhydantoin is 21% less toxic than 5-methyl-5-β-phenylethylhydantoin, it must be ruled out because of the convulsions it causes in low doses. 5-Ethyl-5-benzylhydantoin is but 9% more toxic than 5-methyl-5-β-phenylethylhydantoin, but it is not effective outside the toxic range. 5,5-Cyclopentamethylenehydantoin has about the same toxicity as nirvanol, but has no effective range and causes a considerable increase in the activity of the salivary gland. Several of these new hydantoins of the nirvanol type are now being tested clinically by different medical investigators.

The authors desire to acknowledge the assistance of Mr. W. Saschek of the Department of Biochemistry, Columbia Medical School, New York

[14] The authors desire to express here their appreciation of the assistance given by the Lilly Research Laboratories in carrying out these preliminary pharmacological tests.

City, who made the microanalyses for carbon and hydrogen, which are reported in this paper.

Summary

1. A series of new 5,5-dialkyl-hydantoins has been prepared.
2. A report of a preliminary pharmacological study is included.
3. Several of these hydantoins, 5-methyl-5-β-phenylethylhydantoin, and its 5-ethyl analog, have marked hypnotic properties, and are being subjected to clinical study to determine whether they possess any therapeutic value in the treatment of nervous diseases.
4. Two new α-amino acids related to the hydantoins have been prepared.

NEW HAVEN, CONNECTICUT

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE UNIVERSITY OF ILLINOIS]

THE DIRECTIVE INFLUENCE OF THE ALKYLSULFONAMIDO AND DIALKYLSULFONAMIDO GROUPS

BY R. L. SHRINER, M. T. GOEBEL AND C. S. MARVEL

RECEIVED FEBRUARY 1, 1932 PUBLISHED JUNE 6, 1932

There have been numerous attempts to formulate rules which will allow one to predict the position which a group will take when it enters a monosubstituted benzene ring. Interest in this general problem has been revived by the appearance of two papers[1] which set forth new empirical rules which are apparently less subject to exceptions than are the previous generalizations. It is obvious, however, that a general rule based on theoretical considerations cannot be formulated until all of the common substituents in the ring have been considered. The present work concerns the sulfonamido and disulfonamido groups, which have not been fully considered in the earlier papers.

Hammick and Illingworth[1b] have stated the following orientation rule: "If in the benzene derivative C_6H_5XY, Y is to the right of X in the periodic table, or if, being in the same group, Y is of a lower atomic weight than X, a second atom or group will enter the nucleus in the meta position. In all other cases including that in which XY is a single atom, a second entering group or atom goes to the ortho and para positions." The effect of ionic charges on XY is also discussed and it is pointed out that positive charges direct meta and negative charges direct ortho and para. In the application of their rule they do not clearly indicate what may be expected from a group such as CH_2Cl or $CHCl_2$ where X is C and Y may be H or Cl. In such a case it is obvious that following the rule alone one would predict mixtures of ortho, meta and para isomers. This agrees

[1] (a) Latimer and Porter, THIS JOURNAL, **52**, 206 (1930); (b) Hammick and Illingworth, *J. Chem. Soc.*, 2358 (1930). A review of the earlier literature can be found in these articles.