p-Dimethylaminophenylethynylcarbinol, *o*-Hydroxyphenylethynylcarbinol and Benzylethynylcarbinol each resulted in fair yields for the use of the respective aromatic aldehydes. In no case did the product hold together through a distillation under strongly reduced pressure in an atmosphere of nitrogen. Usually the aldehyde was recovered in good amounts from these cleavages.

Phenylethynylcarbinol.—For use in the Zeitner–Genas method of synthesis of acetylenic carbinols which follows, methylal was made in 75% yield by refluxing 380 g. of powdered paraformaldehyde and 1200 ml. of methanol containing 1.0% dry hydrogen chloride. In a large iron mortar 90 g. of potassium hydroxide was pulverized very easily to a dust under 250 ml. of methylal. In a three-necked flask equipped with a mechanical stirrer was placed the suspension of potassium hydroxide and methylal. On cooling to 0° in an ice–salt-bath about two-thirds of the necessary acetylene was bubbled fast through the solution. A solution of 53 g. of benzaldehyde dissolved in 50 g. of methylal was added dropwise. After continuous cooling, stirring and passage of acetylene for another hour the reaction was interrupted by the addition of 400 ml. of water. The mixture was saturated with salt and the methylal layer was separated. After drying the solution and distilling the methylal, the residue was distilled in an atmosphere of nitrogen. A 35% theoretical yield of phenylethynyl carbinol, b. p. 80–85° (1.5 mm.), 112° (11–12 mm.), was obtained.

When the Zeitner–Genas method was used none of the aromatic aldehydes gave better yields than were obtained by the Jones–McCombie method.

Summary

p-Methoxybenzaldehyde and *o*-methoxybenzaldehyde gave good yields of their corresponding acetylenic carbinols by the Jones–McCombie method. These carbinols yielded their characteristic mercury derivatives.

p-Chlorobenzaldehyde gave a poor yield of *p*-chlorophenylethynylcarbinol.

Phenylacetaldehyde, *p*-dimethylaminobenzaldehyde and salicylaldehyde formed products too fragile to stand distillation.

There was no indication of any reaction when cinnamic aldehyde and 4-ethoxyvanillin were used under the conditions commonly employed.

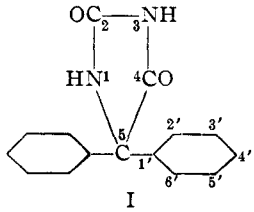
BLOOMINGTON, INDIANA RECEIVED MARCH 6, 1947

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, THE UNIVERSITY OF TEXAS]

Certain 5-Phenyl-5-(Substituted Phenyl)-hydantoins[1]

BY JOSEPH WELDON MELTON[2] AND HENRY R. HENZE

Previous to the introduction of the sodium salt of 5,5-diphenylhydantoin[3] by Merritt and Putnam,[4] no drug was available for the satisfactory control of the *grand mal* type of epilepsy. The fact that 5,5-diphenylhydantoin (I) has rather limited aqueous solubility and the further fact that a *p*H of 11.7 is required to keep its sodium salt in solution indicate that some improvement over this drug should be sought. Although a considerable number of derivatives of I have been made and tested,[5] all have been found to possess decreased anticonvulsant activity. However, in these derivatives, the substituents in one or both of the phenyl groups are located in positions *ortho* or *para* or both *ortho* and *para* to the point of attachment of the phenyl group to the hydantoin nucleus.



I

In general, these hydantoins have been prepared from the appropriately substituted benzophenones by use of the Bucherer procedure[6] as modified in this Laboratory.[7] It was hoped that the introduction of the 3′-hydroxyl group might improve the solubility of the hydantoin derivative and lower the alkalinity of aqueous solutions of the sodium salt. Likewise, the 3′-amino derivative offered the possibility of utilizing the hydrochloride or other salt for administration.

A second group of hydantoins, prepared in this study, contained a 5-phenyl group and a 5-(4-hydroxyphenyl) or 5-(4-aminophenyl) group further substituted by bromine or iodine in the 3′- or 3′,5′ positions. The appropriate halogenated derivatives of 4-aminobenzophenone all formed hydantoins readily, but it was necessary first to prepare 5-(4-hydroxyphenyl)-5-phenylhydantoin for subsequent halogenation in order to obtain the derivatives related analogously to 4-hydroxybenzophenone.

Experimental

Preparation of *m*-Substituted Benzophenones.—Seven metasubstituted benzophenones were prepared by conventional methods; the substituent groupings included the amino,[8] bromo,[9] carboxyl,[10] chloro,[11] hydroxyl,[11]

(1) From the Ph. D. dissertation of J. W. Melton, June, 1946.

(2) Present address: Department of Chemistry, Northwestern State College, Alva, Okla.

(3) Introduced by Parke, Davis and Company as "Dilantin"; recognized in U. S. P. XII as "diphenylhydantoin sodium."

(4) Merritt and Putnam, *Arch. Neurol. Psychiat.*, **39**, 1003 (1938); *J. Am. Med. Assoc.*, **111**, 1068 (1938).

(5) Merritt, Putnam and Bywater, *J. Pharmacol.*, **84**, 67 (1945).

(6) Bucherer and Lieb, *J. prakt. Chem.*, [2] **141**, 5 (1934).

(7) Henze and Long, THIS JOURNAL, **63**, 1941 (1941).

(8) Geigy and Koenigs, *Ber.*, **18**, 2401 (1885).

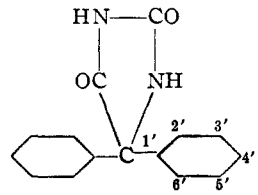
(9) Koopal, *Rec. trav. chim.*, **34**, 153 (1915).

(10) Smith, THIS JOURNAL, **43**, 1920 (1921).

(11) Smith, *Ber.*, **24**, 4044 (1891).

TABLE I

CERTAIN 5-PHENYL-5-(*m*-SUBSTITUTED PHENYL)-HYDANTOINS



Substituents in position 3'	4'	5'	Yield, %	M. p., °C.	Nitrogen, % Calcd.	Found	Halogen, % Calcd.	Found	Carbon, % Calcd.	Found	Hydrogen, % Calcd.	Found
Amino			80	249–250	15.73	15.60			67.51	67.43	4.87	4.80
Bromo			37	209–210	8.46	8.30	24.10	24.06				
Carboxy			71	232	9.46	9.32			64.92	65.03	4.05	3.87
Chloro			45	227–228	9.77	9.68	12.39	12.46				
Hydroxy			60	217–218	10.45	10.36			67.25	67.21	4.48	4.40
Methoxy			75	180	9.93	10.05			67.87	67.90	4.97	4.91
Methyl			70	223	10.52	10.66			72.26	72.18	5.27	5.12
Bromo	Amino		62	244–245	12.14	12.29	23.09	23.03				
Bromo	Amino	Bromo	80	290–291	9.88	9.95	37.59	37.82				
Bromo	Hydroxy		[a]	222	8.07	8.01	23.05	22.86				
Bromo	Hydroxy	Bromo	63	265 dec.[c]	6.58	6.46	37.53	37.20				
Bromo	Methoxy		72	229–230			22.14	21.99				
Iodo	Amino	Iodo	45	249–250 dec.	8.09	8.12	48.91	48.76				
Iodo	Hydroxy	Iodo	90[b]	263 dec.	5.38	5.56	48.84	49.00				

[a] Obtained by hydrobromic acid cleavage of 5-(3-bromo-4-methoxyphenyl)-5-phenylhydantoin. [b] Prepared by iodination of 5-(4-hydroxyphenyl)-5-phenylhydantoin. [c] Melting point markedly effected by rate and duration of heating.

methoxyl[11] and methyl.[12]

Preparation of 5-Phenyl-5-(3-substituted phenyl)-hydantoins.—Several attempts were made to prepare hydantoins from the *m*-substituted benzophenones by the Bucherer procedure[6]; there seemed to be no reaction and the ketones were recovered almost quantitatively. However, successful conversion was achieved by using fused acetamide,[7] as solvent, in a closed container.

The general procedure involved melting 5–10 parts of acetamide in a Pyrex liner and adding ketone, followed by about 1.25 parts of potassium cyanide dissolved in an equal weight of water. To the homogeneous solution was added 3 parts of ammonium carbonate; the monel metal container was closed and placed in an oven heated at 105–140° for twelve–fifteen hours. The cooled reaction mixture was poured over ice (causing separation of some of the hydantoin) and acidified with hydrochloric or acetic acid. If the acetamide solution was poured into water, or was diluted by addition of water, the hydantoin usually appeared as an oil or putty-like mass; by pouring the solution over ice a crystalline product resulted.

The hydantoins were redissolved in alkaline solution, the latter were extracted with ether to recover any unreacted ketone, and were reprecipitated by addition of mineral acid. Final purification was accomplished by crystallization from ethyl alcohol or from acetic acid. Certain data for analyses and physical properties of these hydantoins may be found in Table I.

Halogenation of *p*-Substituted Benzophenones.—Considerable difficulty was experienced in purification of the best grade of *p*-aminobenzophenone available during the war period. Fractional extraction with ether was most successful to effect separation from the *ortho* isomer present. Even greater difficulty was encountered in attempting to purify the available *p*-hydroxybenzophenone. The material used in further synthesis was prepared by diazotizing the *p*-amino compound and replacing the diazonium grouping with the hydroxyl group.

Iodination of the two *p*-substituted benzophenones was carried out by dissolving the compound in dilute hydrochloric acid or in acetic acid solution, and slowly dropping iodine monochloride into the stirred solution; at room temperature the mono-iodo compounds resulted, while warming on the steam cone aided in producing the di-iodo derivatives. In general, the reactions were rapid at first but required some time for complete disappearance of the iodine color after the calculated amount of iodine monochloride had been added. The iodo compounds were recrystallized from acetic acid or from ethyl alcohol.

The brominations were done in chloroform solution. After slow addition of the calculated amount of bromine to the solution, the latter was refluxed until the bromine color was lost, then was evaporated to dryness on a steam cone. The residue was dissolved in hot acetic acid, treated with charcoal, filtered and allowed to cool. The crystalline material was further purified by recrystallization from ethyl alcohol or from acetic acid.

p-Methoxybenzophenone[11] was also dissolved in chloroform and treated with bromine; a 3-bromo derivative (m. p. 79–80°) formed in essentially quantitative yield, but no condition was found which permitted introduction of another atom of bromine.

Anal. Calcd. for $C_{14}H_{11}BrO_2$: Br, 27.45. Found: Br, 27.30.

Preparation of Hydantoins from Halogenated *p*-Aminobenzophenones.—The synthesis of these compounds was similar to that of those derived from the *m*-substituted benzophenones; in general, more fused acetamide was needed because of the decreased solubility of the halogenated ketones. The hydantoins were colorless solids which do not exhibit sharp melting points despite repeated recrystallizations. Pertinent data concerning these new derivatives of diphenylhydantoin are included in Table I. It may be noted that attempts in (molten) acetamide solution to convert 3-bromo-4-hydroxybenzophenone into 5-(3-bromo-4-hydroxyphenyl)-5-phenylhydantoin were unsuccessful in that debromination occurred resulting in

(12) Phenyl *m*-tolyl ketone was first prepared by Ador and Rilliet [*Ber.*, **12**, 2300 (1879)] who reported b. p. 305–311° (723 mm.); Goldschmidt and Stocker, [*ibid.*, **24**, 2807 (1891)] noted b. p. 311–313° (723 mm.); Senff [*Ann.*, **220**, 251 (1883)] recorded b. p. 304–306° with the thermometer bulb in the vapor but b. p. 314–316°, with the thermometer immersed in the vapor. In the present investigation, 10 ml. of this ketone was distilled and found to boil constantly at 316° (cor.) (745 mm.); d^{20}_4 1.095; $n^{20}D$ 1.5970; ΣMR 60.31; MR calcd. 60.48. An oxime was prepared m. p. 118°; Goldschmidt and Stocker reported m. p. 100–101°. *Anal.* Calcd. for $C_{14}H_{13}NO$: N, 6.63. Found: N, 6.71.

production of 5-(4-hydroxyphenyl)-5-phenylhydantoin.[13]

In order to obtain the desired 3'-bromo-4'-hydroxy derivative, 5-(4-hydroxyphenyl)-5-phenylhydantoin was dissolved in glacial acetic acid for bromination, or in cold 5% sodium hydroxide solution for iodination. Little difficulty was encountered in introducing two bromine or two iodine atoms, but no condition was discovered whereby only one atom of halogen was directly substituted into the phenylhydantoin. The 3'-bromo-4'-hydroxy compound was prepared by cleaving the methoxyl group in 5-(3-bromo-4-methoxyphenyl)-5-phenylhydantoin by refluxing with 48% hydrobromic acid solution; all attempts to prepare the mono-iodo analog were unsuccessful.

Summary

1. This investigation includes the synthesis of seven examples of 5-phenyl-5-*m*-substituted phenylhydantoins. These hydantoins are the first to be prepared from meta substituted benzophenones.

2. Four halogenated derivatives of *p*-aminobenzophenone and three halogenated derivatives of *p*-hydroxybenzophenone have been prepared; of these four have not previously been reported.

3. These halogenated derivatives of *p*-aminobenzophenone form hydantoins readily; to obtain the corresponding hydantoin derivatives of *p*-hydroxybenzophenone, it was necessary first to synthesize 5-(4-hydroxyphenyl)-5-phenylhydantoin and to subject the latter to bromination or iodination.

(13) A. F. Isbell, Ph. D. dissertation, University of Texas, 1943.

AUSTIN, TEXAS RECEIVED MARCH 17, 1947

[CONTRIBUTION FROM THE CENTRAL RESEARCH DEPARTMENT, MONSANTO CHEMICAL COMPANY]

Synthesis of Aromatic Phosphonic Acids and Their Derivatives. I. The Derivatives of Benzene, Toluene and Chlorobenzenes

BY GENNADY M. KOSOLAPOFF AND W. FREDERICK HUBER

The Michaelis[1] modification of the Friedel–Crafts reaction used for the preparation of aromatic dichlorophosphines from which a wide variety of aromatic derivatives of phosphorus can be obtained, gives very poor yields, usually below 20–25% and often below 10%. It has been seen readily that this is due to the loss, to all practical purposes, of the bulk of the chlorophosphines in the so-called complex layer during the extraction with petroleum ether. This layer of viscous matter comprises the complex between the aluminum chloride and the chlorophosphines and cannot be resolved into components by simple hydrolysis because of the formation of extremely stable aluminum salts of the resulting acids. The problem was thus seen to lie in a successful break-down of the complex, to be followed by the isolation of the phosphorus derivatives in a more manageable form than that presented by the chlorophosphines. Since trivalent phosphorus compounds react vigorously with halogens, such as chlorine, to form very stable halogen derivatives of pentavalent phosphorus, it was felt that halogenation, or specifically chlorination, of the reaction mixture would effect the desired break-down of the aluminum chloride complex. However, since the hydrolysis of such a mixture would still lead to the formation of stable and untractable aluminum salts, it was obviously necessary to convert the chlorophosphines into relatively stable derivatives before the removal from the reaction mixture of the undesired aluminum chloride by the most logical method, *i.e.*, by washing with water. The choice of the desirable derivative was made in favor of the esters, for reasons of economy and ease of handling. The application of the above principles resulted in a significant improvement of the Michaelis reaction, which made it possible to effect the preparation of the esters of aromatic phosphonic acids in excellent yields, without the necessity of handling sensitive and malodorous intermediates. It was also found that the reaction can be made to yield compounds of the type R_2PO_2H, besides those of the type RPO_3H_2. This fact arises from the disproportionation of the initially-formed dichlorophosphines, which fact was observed by Michaelis as occurring on heating dichlorophosphines to high temperatures in sealed tubes. The presence of aluminum chloride apparently catalyzes this reaction and leads to the formation of di-substituted derivatives at ordinary reflux temperatures. The esters, isolated by distillation, can be readily converted into the corresponding acids by refluxing with concentrated hydrochloric acid, followed by evaporation in the cases of soluble types.

(1) Michaelis, *Ber.*, **12**, 1009 (1879).

Experimental

The general procedure used is given below. The hydrocarbon was mixed with the desired amounts of phosphorus trichloride and aluminum chloride and the mixture was refluxed, with protection against atmospheric moisture. The excess of phosphorus trichloride was then removed under reduced pressure, with stirring, at a temperature not in excess of 50–60°. The residual mass was diluted with one to two volumes of dry tetrachloroethane (other chlorinated solvents are somewhat less satisfactory) and was treated with dry chlorine, with good agitation and cooling by means of ice-water, until the absorption was complete; this generally required one to two hours for molar runs. An excess of alcohol (five moles per mole of the hydrocarbon) was then added slowly to the stirred and cooled mixture, with application of reduced pressure by means of a water pump to remove hydrogen chloride. The esterification is most satisfactorily conducted at about 15°. The reaction mixture was then treated with a mixture of ice and hydrochloric acid and the organic layer was