phenyl, and 3,4-methylenedioxyphenyl, have been treated with maleic anhydride.

2. Structure determinations carried out on the adducts formed in the first two cases prove that maleic anhydride reacts preferentially with the aliphatic side chain. In these two examples the aryl group occupies the *cis* position with regard to the adjacent carbonyl group.

3. Attempts to prove the structure of the adduct from maleic anhydride and 3,4-methylenedioxyphenylallylcarbinol failed.

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

Synthesis of 5-(Substituted-methyl)-5-phenethylhydantoins[1]

BY HENRY R. HENZE AND CHARLES B. HOLDER[2]

Recently, we[3] reported the synthesis from 1-chloro-4-phenyl-2-butanone of certain derivatives of 5-phenethylhydantoin in which the basicity of the latter had been increased through utilization of a 5-dialkylaminomethyl-, 5-(4-morpholinyl)-methyl-, or 5-(N-ethyl-N-phenylaminomethyl)-grouping. Since, upon being tested,[4] these hydantoins of enhanced basicity were found not to possess useful pharmacological activity, it was decided to prepare related compounds in which the 5-methyl grouping had been altered through introduction of an acidic (carboxyl) radical, or of derivatives of such acidic grouping. Hydantoins of this type are homologs of certain 5-phenylhydantoins previously prepared in this Laboratory.[5] The latter were synthesized from keto esters and keto nitriles containing the benzoyl group, these intermediates being easily attainable by appropriate application of the Claisen condensation. However, when preparation of the desired keto ester or keto nitrile requires utilization of two compounds each capable of self-condensation, employment of the Claisen condensation is not wholly satisfactory. In the present instance, since preparation of ethyl hydrocinnamoylacetate or ethyl hydrocinnamoylacetonitrile would involve use of such self-condensable intermediates, an alternate route was thought to be desirable. It was visualized that perhaps 1-chloro-4-phenyl-2-butanone could be converted into 5-phenethyl-5-hydantoinacetonitrile by utilization of the Bucherer[6] method if additional potassium cyanide was used. Such conversion, involving reaction of cyanide with both halogen and carbonyl groups in a chloro ketone, has not previously been reported. No difficulty was to be anticipated in subsequent conversion of the nitrile into other derivatives of 5-phenethyl-5-hydantoinacetic acid.

Interaction of 1-chloro-4-phenyl-2-butanone with a mixture of at least two equivalents of potassium cyanide and three of ammonium carbonate did yield some of the anticipated substituted hydantoinacetonitrile. However, this conversion represented neither the only reaction in which the chloro ketone was involved, nor involved the major portion of that compound. There was produced in larger yield another substance, probably of composition $C_{21}H_{20}N_2$, the structure of which has not yet been established. With less than two equivalents of cyanide, the chloro ketone yielded little or no hydantoin, indicating that conversion of the carbonyl group into the hydantoin nucleus occurs subsequent to reaction of the halogen.

Ethyl 5-phenethyl-5-hydantoinacetate was synthesized also, although in poorer yield, from ethyl hydrocinnamoylacetate, since our samples of 1-chloro-4-phenyl-2-butanone had physical properties differing essentially from those reported elsewhere.[7] The properties of the hydantoinacetate, prepared by either method, were uniformly the same, hence the identity of the chloroketone, and of its chlorohydrin precursor, is confirmed.

A study of the material melting at 96° [$C_{21}H_{20}N_2$] obtained as a by-product in the preparation of 5-phenethyl-5-hydantoinacetonitrile, indicates that it is formed from interaction of two molecules of the chloro ketone with potassium cyanide and ammonium carbonate, but not from the action of either of the latter alone. The product must be heterocyclic, possess aromatic properties and but one active hydrogen atom. It is quite resistant, under usual conditions of treatment, toward hydrolysis, oxidation and reduction.

Experimental

Application of Bucherer Method to 1-Chloro-4-phenyl-2-butanone.—To a flask equipped with a condenser were added 40 g. (0.22 mole) of the chloro ketone, 31.4 g. (0.48 mole) of potassium cyanide, 69.4 g. (0.35 mole) of ammonium carbonate, and 550 cc. of 65% alcohol. After

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[1] From Part II of the Ph.D. dissertation of C. B. Holder, June, 1941.

[2] Present address: Texas Company, Beacon, N. Y.

[3] Henze and Holder, THIS JOURNAL, **63**, 1943 (1941).

[4] Through the courtesy of Parke, Davis and Company three of these compounds have received preliminary testing for possible pharmacological activity with results as follows

5-($R-CH_2-$)-5-PHENETHYLHYDANTOINS

R-	M. L. D. (mg./kg.)	Activity Analgesic	Hypnotic	Dose, (mg./kg.) by S. T.	Anticonvulsic
Diethylamino	100	*a*	None	50	None
Di-*n*-propylamino	350	*a*	None	95[b]	None
4-Morpholinyl	400	*a*	None	250	None

[a] Little if any analgesic activity. [b] At the level of 110 mg./kg. the cat was dead at the end of two hours.

[5] Henze and Rogers, THIS JOURNAL, **63**, 2190 (1941).

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

[7] See ref. 3, pp. 1943–1944.

heating at 58–60° for twenty hours, upon chilling scarcely any solid appeared; evaporation of most of the alcohol under reduced pressure caused the separation of 18.1 g. of a dark red viscous oil which became semi-solid on cooling.[8] After decantation from this oil, the solution was neutralized yielding 24 g. of crude hydantoin. One crystallization from water gave 14 g. (26% yield) of a product melting at 184–185° (cor.); after successive recrystallizations from water, alcohol and ethyl acetate, 5-phenethyl-5-hydantoinacetonitrile melted at 188–189° (cor.). That the course of the reaction is dependent, apparently, upon minor variations in concentration and reaction time is shown by the fact that in six preparations the yield varied between 45% and 19%, based on the weight of crude product and averaged 39%.

Anal. Calcd. for $C_{13}H_{13}N_3O_2$: C, 64.19; H, 5.39; N, 17.37. Found: C, 64.48; H, 5.30; N, 17.20.

This reaction was repeated with the sole exception that but 15.7 g. (0.24 mole) of potassium cyanide was used. There resulted the formation of the compound melting at 96° in somewhat larger yield, very little of the hydantoinacetonitrile derivative, and, in addition, 22 g. of a solid whose melting point could not be brought to constant melting point through recrystallization; the crude material melted near 160°, and after successive recrystallizations at about 200, 210, 220 and 230°. The material was not soluble in 20% sodium hydroxide solution; hence, was not a hydantoin derivative.

Preparation of Ethyl 5-Phenethyl-5-hydantoinacetate: A. From 5-Phenethyl-5-hydantoinacetonitrile.—After passing dry hydrogen chloride into a hot solution of 2.6 g. of this nitrile in 20 cc. of ethyl alcohol under reflux for two hours, 5 cc. of concentrated hydrochloric acid was added and the heating continued for two hours longer. Upon chilling, 1.8 g. (58% yield) of the crude ethyl ester was obtained. Other small scale preparations gave yields varying between 47 and 70% of the theoretical quantity. Recrystallization from diluted alcohol and from benzene yielded the pure ester melting at 156.7–157.7° (cor.).

Anal. Calcd. for $C_{15}H_{18}N_2O_4$: C, 62.07; H, 6.25; N, 9.65. Found: C, 62.31; H, 6.39; N, 9.57.

B. From Ethyl Hydrocinnamoylacetate.—To a solution of 35.8 g. (0.275 mole) of ethyl acetoacetate in 500 cc. of dry benzene was added 5.43 g. (0.236 gram atom) of sodium and the mixture was placed on a steam cone for twenty hours. Next, 39.8 g. (0.236 mole) of hydrocinnamoyl chloride was added slowly, and this mixture was heated on the steam cone for six hours. The reaction mixture was cooled, added to ice-water, and the aqueous layer was removed. The benzene solution was extracted with 20 cc. of sodium bicarbonate solution, dried over anhydrous sodium sulfate, and the benzene removed by distillation. An attempted distillation of the residual oil, under 6 mm. pressure and with a bath temperature of 190°, yielded four small fractions of distillate, totalling but 5 g. in weight, which were not homogeneous and seemed to contain very little of the desired ester. A further attempt to distil an additional small fraction at 3 mm. pressure with bath temperature at 230° was unsuccessful. The two fractions apparently most nearly homogeneous had properties as follows: $n^{20}\mathrm{D}$ 1.5271, 1.5239; d^{20}_{4} 1.0718; MR observed 75.16, 78.31; ΣMR 69.55 (keto), 70.59 (enol). Since the ethyl α-hydrocinnamoylacetate present did not seem isolable under these conditions of fractionation, hydrolysis was attempted without isolation of the ester.

The four fractions and the residue from distillation were combined and added to 32 g. of ammonium chloride and 10 cc. of concentrated ammonium hydroxide solution in 150 cc. of water at 50°. After twenty minutes, the mixture was cooled in an ice-bath and extracted with ether. After removal of the ether, distillation of a small portion of the residual oil yielded a very small amount of liquid; b. p. 135–137° (2.5 mm.); $n^{20}\mathrm{D}$ 1.5232; d^{20}_{4} 1.0845. Since this distillate was apparently composed largely of the same material as that before the attempted hydrolysis, another effort by a different procedure was made.

The material was now warmed for twenty hours on a steam cone with a four-fold quantity of 75% acetic acid. The mixture was then poured into a large volume of water and the oily layer was separated, dried over anhydrous sodium sulfate, and distilled under diminished pressure. There was collected 5 cc. of material; b. p. 127–134° (4 mm.); $n^{20}\mathrm{D}$ 1.5058; d^{20}_{4} 1.0679; MR observed 61.18; MR 60.30 (keto), 61.35 (enol).

In a flask was placed 3.9 cc. of this but partially purified ethyl hydrocinnamoylacetate, 2 g. of potassium cyanide and 10 g. of ammonium carbonate in 45 cc. of 55% alcohol. After heating for ten hours at 58–60°, addition of water and cooling, 2.2 g. of solid melting at 142–145° separated; an additional 0.6 g. was obtained after neutralization of the mother liquor. The yield of crude hydantoin amounted to 55% of the theoretical amount. Five successive recrystallizations brought the melting point to 155.7–156.7°. The melting point of a mixture of this material with that (m. p. 156.7–157.7°) from esterification of 5-phenethyl-5-hydantoinacetonitrile was 156.2–157.2°.

Anal. Calcd. for $C_{15}H_{18}N_2O_4$: C, 62.07; H, 6.25; N, 9.65. Found: C, 62.61; H, 6.10; N, 9.34.

Preparation of 5-Phenethyl-5-hydantoinacetamide.—To 35 cc. of concentrated ammonium hydroxide solution was added 3.85 g. of ethyl 5-phenethyl-5-hydantoinacetate, and the mixture was allowed to stand for two weeks in a closed container. Evaporation of most of the solution caused separation of 2.04 g. of crude amide, which, after crystallization from diluted alcohol, gave 1.80 g. (52% yield) of solid melting at 224.5–227.0°. Recrystallizations from water resulted in a constant melting point of 228.7–229.7° (cor.). The amide is essentially insoluble in ether, is slightly soluble in acetone and in water, and is quite soluble in alcohol.

Anal. Calcd. for $C_{13}H_{15}N_3O_3$: C, 59.76; H, 5.79; N, 16.08. Found: C, 59.92; H, 5.61; N, 16.15.

Preparation of 5-Phenethyl-5-hydantoinacetic Acid: A. From the Ethyl Ester.—Two grams of crude ethyl 5-phenethyl-5-hydantoinacetate was dissolved in a slight excess of 10% potassium hydroxide solution, the solution was cooled, and acidified by addition of 6 N hydrochloric acid. Hardly any precipitate formed immediately, but upon standing there separated 0.87 g. (48% yield) of solid melting at 207.5–210.5°. After several recrystallizations from water, the melting point was 213.0–214.5° (cor.).

Anal. Calcd. for $C_{13}H_{14}N_2O_4$: C, 59.53; H, 5.38; N, 10.68. Found: C, 59.83; H, 5.39; N, 11.06.

B. From the Nitrile.—A suspension of 1.7 g. of 5-phenethyl-5-hydantoinacetonitrile in 15 cc. of 25% hydrochloric acid was heated under reflux for twenty hours on a steam-cone. The mixture was then heated to boiling, filtered, and the semi-solid residue was extracted with boiling water until further extraction yielded no solid on cooling. From the combined filtrates there separated 0.80 g. (44% yield) of the acid melting at 211.5–212.5°.

C. From the Amide.—By warming 5-phenethyl-5-hydantoinacetamide with 6 N hydrochloric acid, the crude acid, melting at 204–207°, was obtained.

In general, the properties of the hydantoinacetonitrile, the acid, the amide and the ethyl ester are of the type to be expected of compounds containing the acidic heterocyclic nucleus and the additional functional group. However, it may be pointed out that ethyl 5-phenethyl-5-hydantoinacetate is hydrolyzed very much more readily than are the esters of 5-phenyl-5-hydantoinacetic acid.[5] Thus, while the former is hydrolyzed by brief contact with cold, dilute sodium hydroxide, the latter are reprecipitated by acidification of their solution in alkalies.

$C_{21}H_{20}N_2$ (?).—The material melting at 96°, a by-product of the interaction of 1-chloro-4-phenyl-2-butanone with excess potassium cyanide and ammonium carbonate, is quite soluble in alcohol, ether, acetone, benzene, chloroform, carbon tetrachloride and ethyl acetate, but is insoluble in water. Petroleum ether proved to be the best solvent for its recrystallization; the compound dissolves

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[8] Petroleum ether extraction of the oil yielded a solid, melting at 96° (cor.), which will be considered subsequently.

to the extent of about 1 g. in 100 cc. of the boiling solvent, but is almost insoluble in the cold.

Anal. Found: C, 83.99, 83.95, 83.89, 84.10, average 83.98; H, 6.84, 6.69, 6.78, 6.84, average 6.79; N, 8.90, 8.92, 9.14, 9.25, average 9.05; molecular weight (Rast method), 287, 303. Calcd. for $C_{21}H_{20}N_2$: C, 83.96; H, 6.79; N, 9.33; mol. wt., 300.4. For $C_{22}H_{22}N_2$: C, 84.04; H, 7.05; N, 8.91; mol. wt., 314.4.

A. Attempted Hydrolysis.—After heating 0.1448 g. of the compound in 10 cc. of concentrated hydrochloric acid for one hour at 70–90°, there was recovered 0.1450 g. of material of unchanged melting point. After refluxing overnight at the boiling point of the acid, most of the material was recovered unchanged. Likewise, more than 90% of the material was recovered, with but slightly lowered melting point, after refluxing the compound for six days in 10% aqueous potassium hydroxide solution. Similar lack of hydrolysis occurred through heating in a solution of potassium hydroxide in absolute alcohol.

B. Attempted Reduction.—After exposure of 0.5023 g. of the material melting at 96° to hydrogen in the presence of the Adams platinum catalyst for five days, there was recovered 0.284 g. of recrystallized material melting at 90–93°; the melting point of a mixture with the original compound was 94–95°. The initial compound was unaffected by action of tin and hot concentrated hydrochloric acid.

C. Attempted Oxidation.—Even after exposure of the compound to the action of a saturated solution of potassium permanganate in acetone at 55° for one week, solid, melting at 83–85°, was recovered and, upon purification, proved to be unchanged material. However, the action of an alkaline solution of potassium permanganate[9] resulted in the production of benzoic acid.

D. Bromination.—Preliminary trial indicated that the product melting at 96° decolorized a benzene solution of bromine, with evolution of hydrogen bromide, much more readily than did a benzene solution of 1-chloro-4-phenyl-2-butanone or 5-phenethyl-5-hydantoinacetonitrile.

Therefore, to 1.0 g. (0.0033 mole based on $C_{21}H_{20}N_2$) of the compound in benzene solution at room temperature was added a bromine solution containing 0.655 g. (0.0041 mole) of bromine. During most of the addition, the color due to bromine disappeared and hydrogen bromide was evolved. The solvent was removed by evaporation and the solid residue was recrystallized from diluted alcohol to yield 1.15 g. of material melting at 80–90°. Two further recrystallizations produced 0.89 g. melting at 101–102° (cor.).

Anal. Calcd. for $C_{21}H_{19}BrN_2$: mol. wt., 379.4; C, 66.50; H, 5.05; Br, 21.07; N, 7.39. Found: mol. wt. (Rast), 365; C, 66.74; H, 5.12; Br, 21.08; N, 7.48.

E. Action of Alcoholic Hydrogen Chloride.—Two grams of the compound melting at 96° was dissolved in 25 cc. of ethanol and the solution was heated under reflux on a steam-cone for twenty hours with continuous introduction of dry hydrogen chloride. Upon cooling, a semi-solid precipitate formed but could not be made to solidify completely. Hence, 20 cc. of concentrated hydrochloric acid was added and heating was continued for five hours. Subsequent cooling caused the separation of a small amount of solid and relatively a larger amount of an oily liquid. The latter, halogen-free but containing nitrogen, was heated for twelve hours with 30 cc. of 10% solution of sodium hydroxide in 50% alcohol. Upon cooling, there was obtained 1.35 g. of a solid, melting at 141–144°, which, after five recrystallizations from diluted alcohol and from benzene, produced 0.82 g. of material melting at 153.2–154.2° (cor.). The analytical data indicated that this treatment had caused hydration of the initial product.

Anal. Calcd. for $C_{21}H_{22}N_2O$: C, 79.21; H, 6.96; N, 8.80. Found: C, 79.22; H, 6.97; N, 8.68.

Summary

1. By slight modification of the Bucherer procedure, a 5,5-disubstituted hydantoin has been synthesized from an α-chloroketone. From the 5-phenethyl-5-hydantoinacetonitrile have been prepared the corresponding hydantoinacetic acid, its ethyl ester and its amide.

2. As a by-product in the synthesis of the hydantoinacetonitrile there was obtained a neutral, chemically rather non-reactive material, probably $C_{21}H_{20}N_2$, the structure of which is unknown, but certainly is not that of a hydantoin.

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(9) Shriner and Fuson, "Identification of Organic Compounds," John Wiley and Sons, Inc., New York, N. Y., 1935, p. 139.

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF MOUNT HOLYOKE COLLEGE]

Addition of Grignard Reagents to α,β-Unsaturated Aldehydes and Ketones. I. *trans*-3-Hepten-2-one

BY MARTHA E. SMITH, BARBARA CHASE[1] AND RUTH RHODES[1]

For an investigation of the influence of steric factors in determining the mode of addition of the Grignard reagent to the conjugated system present in α,β-unsaturated ketones, the extent of 1,4-addition of three different Grignard reagents to *trans*-3-hepten-2-one has been studied. This ketone has been prepared by dehydration of the corresponding ketol, 4-hydroxy-2-heptanone. The ketol was prepared according to the method of Eccott and Linstead.[2] The preparation of the *cis* isomer by the direct condensation of *n*-butyraldehyde and acetone has been reported by Eccott and Linstead,[2] but Powell and Ballard[3] have indicated that the product obtained in this reaction under the conditions used by Eccott and Linstead consists of a mixture of the unsaturated aldehyde, 2-ethyl-2-hexenal, and the *trans* form of 3-hepten-2-one. This reaction and the behavior of the product with Grignard reagents is under further investigation in this Laboratory.

According to Grignard and Dubien,[4] the reaction of 3-hepten-2-one with methyl-, ethyl-, *n*-propyl- and *n*-butylmagnesium halides gave only the 1,2-addition product, with no evidence of any 1,4-addition, while Colonge[5] reported 40% satu-

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(1) Part of the experimental work was done by Barbara Chase and Ruth Rhodes in partial fulfillment of the requirements for the degree of Master of Arts at Mount Holyoke College.

(2) Eccott and Linstead, *J. Chem. Soc.*, 905 (1930).

(3) Powell and Ballard, THIS JOURNAL, **60**, 1914 (1938).

(4) Grignard and Dubien, *Ann. chim.*, **2**, 282 (1924).

(5) Colonge, *Bull. soc. chim.*, [5] **3**, 413 (1936).