

neutralizing exactly with sodium hydroxide, a product was obtained which was soluble, however, in more alkali. This solid was filtered off and washed with water; yield 1 g. After several recrystallizations from dilute alcohol the product melted at 191–192° (dec., cor.).

Anal. Calcd. for $C_{10}H_{13}N_3O_2$: N, 20.09; C, 57.43; H, 7.18. Found: N, 20.14; C, 57.39; H, 8.19.

2-N⁴-Acetylsulfanilamidopyrimidines.—The N⁴-acetylsulfanilamides were prepared in 67–97% yields by adding a small excess of acetyl sulfanilyl chloride to the aminopyrimidine suspended in dry pyridine, the weight of the latter being equal to that of the total solids. Solution took place with evolution of heat and the reactions were completed by heating at 60° for one-half to one hour. The crude derivatives obtained by pouring the dark solutions into ice water or dilute hydrochloric acid were dissolved in one equivalent of aqueous sodium hydroxide, decolorized,

and reprecipitated by addition of excess of hydrochloric acid.

Hydrolysis.—The N⁴-acetyl group was hydrolyzed by refluxing 0.5–1.0 molar solutions containing 2.5 equivalents of sodium hydroxide for three hours. The solutions were decolorized and the free amines precipitated by acidification to pH 6. Yields of 80–99% were obtained.

Summary

The preparation of six new 2-sulfanilamidopyrimidines and their N⁴-acetyl derivatives is reported.

The synthesis of 2-amino-4-methyl-5-*n*-amylpyrimidine is described and evidence for its structure is presented.

PHILADELPHIA, PENNA.

RECEIVED APRIL 28, 1941

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

The Preparation of Certain 5-Acetates and 5-Acetamides of 5-Phenylhydantoin¹

BY BURL G. ROGERS² WITH HENRY R. HENZE

Previous attempts in this Laboratory to prepare derivatives of hydantoin possessing valuable physiological activity have been restricted largely to variation in alkyl, alkoxyalkyl, aryl, or aryl-oxyalkyl groupings attached to the 5-position of the heterocycle. In broadening this investigation to include additional groups, it was with the knowledge that simple aliphatic acids exhibit scarcely any narcotic action and, therefore, the introduction of a carboxyl group into the molecular structure tends to diminish hypnotic effect. However, esterification of the carboxyl group, or conversion of the latter into an amide, restores or increases physiological activity. Hence it seemed desirable to synthesize certain hydantoin derivatives in which ester or amide groupings were present in addition to a phenyl grouping, which, in hydantoins such as Nirvanol and Dilantin, appears to be favorable for hypnotic effect and essential for maximum anticonvulsant activity.

Ethyl 5-Phenyl-5-hydantoinacetate.—A mixture of 19.2 g. of ethyl benzoylacetate³ with 13 g. of potassium cyanide and 45.5 g. of ammonium carbonate cubes was dissolved in 350 cc. of 60% alcohol and warmed for ten hours at 58–62°. After chilling, the hydantoin derivative was precipitated with hydrochloric acid and on recrystallization

from diluted alcohol gave fine white crystals; m. p. 139–140° (cor.) in 60% yield. The action of concentrated ammonium hydroxide solution at room temperature for one week converted this ester into the amide.

5-Phenyl-5-hydantoinacetic Acid.—Twenty grams of the ethyl ester was boiled for three hours with 50 cc. of 20% hydrochloric acid. Recrystallization from water yielded 16.5 g. (87%) of crystalline acid; m. p. 261.5–262.5° (cor.).

Esters of 5-Phenyl-5-hydantoinacetic Acid.—Additional esters were obtained by suspending the acid in an excess of an appropriate alcohol (methyl, *n*-propyl, allyl, benzyl) or ethylene glycol and saturating the mixture with dry hydrogen chloride until complete solution of the acid had occurred. The solution was heated under reflux for two to three hours, the excess alcohol removed by evaporation, and the solid residue was recrystallized from dilute alcohol. The phenyl ester was secured by interaction of the acid chloride and phenol in the presence of pyridine using dry tetrachloroethylene as solvent.

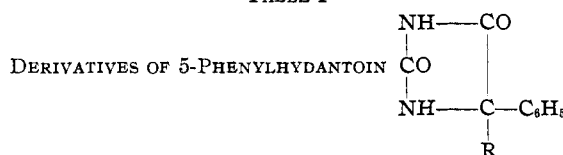
Substituted Amides of 5-Phenyl-5-hydantoinacetic Acid.—Contact of the ethyl ester for ten days at room temperature with a 33% aqueous solution of ethylamine gives rise to the ethyl amide which is insoluble in acetone, dioxane, ethanol, chloroform and benzene, but can be recrystallized from dilute alcohol. Attempts to crystallize the ethyl amide from glacial acetic acid give the hydantoinacetic acid. Attempts to prepare other substituted amides from the ethyl ester and the appropriate amine resulted in failure, but these amides were prepared by converting the hydantoinacetic acid compound into the acid chloride by means of thionyl chloride and by treating the latter, without purification, with 2 equivalents of an amine such as diethylamine, aniline and morpholine. The amides were recrystallized from diluted alcohol and are soluble in acetone and alcohol, but relatively insoluble in water

(1) Presented before the Division of Organic Chemistry at the 99th meeting of The American Chemical Society at Cincinnati, Ohio, April 8–12, 1940.

(2) From the Ph.D. dissertation of B. G. Rogers, June, 1940.

(3) Dorsch and McElvain, *THIS JOURNAL*, **54**, 2960 (1932).

TABLE I



-R	M. p., ° C., cor.	Yield, %	Nitrogen, %	
			Calcd.	Found
-CH ₂ COOH	261.5-262.5(dec.)	87 ^a	11.97	11.76
-CH ₂ COOCH ₃	223.0-224.0	63 ^b	11.29	11.37
-CH ₂ COOC ₂ H ₅	139.0-140.0	60 ^c	10.68	10.89
-CH ₂ COOC ₃ H _{7-n}	105.5-107.0	85 ^b	10.14	10.16
-CH ₂ COOC ₃ H _{11-i}	126.5-127.5	77 ^b	9.21	9.39
-CH ₂ COOC ₂ CH=CH ₂	112.5-113.5	51 ^b	10.22	10.32
-CH ₂ COOCH ₂ CH ₂ OH	127.0-128.0	60 ^b	10.07	10.01
-CH ₂ COOCH ₂ C ₆ H ₅	160.0-161.0	73 ^b	8.64	8.73
-CH ₂ COOC ₆ H ₅	226.0-227.0	39 ^d	9.03	9.03
-CH ₂ CONH ₂	255.5-256.5(dec.)	77 ^a	18.02	17.80
-CH ₂ CONHC ₂ H ₅	247.0-248.0(dec.)	33 ^a	16.01	16.08
-CH ₂ CON(C ₂ H ₅) ₂	223.0-223.5	65 ^d	14.53	14.60
-CH ₂ CON $\begin{matrix} \text{CH}_2\text{CH}_2\text{O} \\ \text{CH}_2\text{CH}_2 \end{matrix}$	168.0-170.0 ^f	70 ^d	13.86	13.91
-CH ₂ CONHC ₆ H ₅	269.0-270.0(dec.)	62 ^d	13.59	13.50
-CH ₂ CN	251.5-252.5(dec.)	9 ^e	19.53	19.81
-CH(CH ₃)COOC ₂ H ₅	241.0-242.0	32	10.14	10.39
-CH(CH ₃)COOH	271.5-273.0	84	11.29	11.05

^a Yield based on ethyl 5-phenyl-5-hydantoinacetate. ^b Yield based on 5-phenyl-5-hydantoinacetic acid. ^c Yield based on benzoylacetic ester. ^d Yield based on 5-phenyl-5-hydantoinacetyl chloride. ^e Yield based on benzoylacetonitrile. ^f On continued heating above this temperature, the compound resolidifies and melts at 255.5-257.0°.

They are precipitated unchanged from solution in cold, dilute alkali by addition of a mineral acid.

Preparation of 5-Phenyl-5-hydantoinacetonitrile.—This compound was prepared from benzoylacetonitrile,³ using 14.5 g., mixed with 13 g. of potassium cyanide and 45.5 g. of ammonium carbonate dissolved in 65% ethyl alcohol. Although the solution was heated for twenty-four hours at 58-62°, reaction was incomplete and 12 g. of benzoylacetonitrile was regained (83% recovery). There was obtained 1.9 g. of the cyanohydantoin, representing a yield of only 9% based on the nitrile available but 51% conversion of the amount of nitrile not recovered.

Preparation of 5-Phenyl-5-(α -cyanoethyl)-hydantoin.—An attempt was made to obtain this compound from inter-action of α -benzoylpropionitrile,³ potassium cyanide and ammonium carbonate in 70% alcohol solution at 58-62° for twenty-six hours, but more than 90% of the nitrile was recovered unaltered.

A second attempt was made to prepare this hydantoin-nitrile by heating the reactants in a bomb together with

carbon dioxide under pressure,⁴ but, again, 90% of the keto nitrile was recovered.

Preparation of 5-Phenyl-5-(α -carbethoxyethyl)-hydantoin.—By warming a solution of ethyl α -benzoylpropionate,³ potassium cyanide and ammonium carbonate in 50% ethyl alcohol for ten hours at 58-62°, a 32% yield of the desired product was obtained.

Preparation of 5-Phenyl-5-(α -carboxyethyl)-hydantoin.—The acid was obtained by hydrolyzing its ester by boiling with 1:1 hydrochloric acid.

Summary

The synthesis has been reported of 5-phenyl-hydantoinacetic acid and sixteen of its derivatives. The latter include examples of esters, amides and nitriles.

AUSTIN, TEXAS

RECEIVED MAY 12, 1941

(4) Bergs, German Patent 566,094 (Dec. 1, 1932).