obtained analogously to the previously described ethiodides. It crystallizes from the ether-alcohol mixture in yellow needles melting at 201°.

Summary

1. A modified method is given for preparing the p-nitrophenyl alkyl ethers.

2. A method is described for preparing the p-aceto-aminophenyl alkyl ethers from p-aminophenol.

3. The following new compounds have been prepared: the p-nitrophenyl butyl-, and p-nitrophenyl iso-amyl ethers; the p-aceto-amino-phenyl butyl-, p-aceto-aminophenyl allyl-, p-aceto-aminophenyl iso-butyl, p-aceto-aminophenyl iso-amyl ethers; the p-aminophenyl butyl- and p-aminophenyl iso-amyl ethers; and the sulfates of the p-aminophenyl alkyl ethers.

4. Several 6-alkyloxyquinaldines, and their ethiodides, have been prepared: 6-propyloxy-, 6-allyloxy-, 6-butyloxy-, 6-iso-butyloxy-, and 6-iso-amyloxyquinaldines.

We are indebted to Mr. B. V. Bush and Mr. P. A. Benedict for the analytical data given in this paper, and to Mr. S. Bissel for a part of the experimental work.

ROCHESTER, NEW YORK

# RESEARCHES ON HYDANTOINS. SYNTHESIS OF THE SOPORIFIC, 4,4-PHENYLETHYL-HYDANTOIN(NIRVANOL)
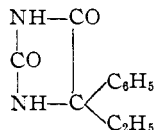
BY WILLIAM T. READ[1]

Pyrimidine derivatives have met with wide use as pharmaceuticals. The most important are the valuable soporifics, diethyl-barbituric acid (I) or Veronal, and phenylethyl-barbituric acid (II) or Luminal. As far as the writer is aware, the only hydantoin derivative of proved value as a soporific is 4,4-phenylethyl-hydantoin (III), now known by the trade name of Nirvanol.
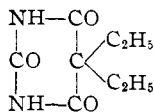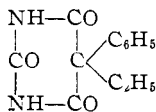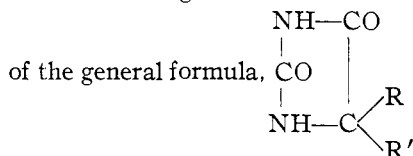

I	II	III

Since the grouping RR'—C—CO—NH—CO—NH— is common to the dialkyl pyrimidines of the barbituric acid series and the hydantoins sub-
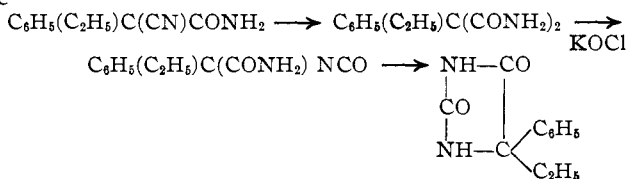
stituted in the 5 and 4 positions, respectively, the same general physiological properties might be expected. In those compounds whose substituents are aliphatic radicals, there is not a parallel physiological action. Diethyl hydantoin has no sleep-producing power,[2] while diethyl-barbituric acid has a very pronounced effect.[3] Phenylethyl-barbituric acid is considerably more active than is the diethyl derivative, but the dosages of the two required to produce the same effect stand in the ratio of $3:5$.[4] However, with the substitution of phenyl for ethyl in the hydantoin, there is the appearance of very active sleep-producing properties.[5]

Nirvanol began to be used as a drug in 1917, and it now appears to be generally accepted as a successful addition to the series of compounds which produce sleep. Since it would appear that the valuable properties of this hydantoin might be found in other hydantoins, and the methods of synthesis applicable to its manufacture might also be made use of in the preparation of other hydantoin derivatives, an investigation of 4,4-phenylethyl-hydantoin has been undertaken.

The following methods have been applied to the synthesis of hydantoins

$$\text{of the general formula,}\quad \begin{array}{c} \text{NH—CO} \\ |\qquad | \\ \text{CO}\qquad | \\ |\qquad | \diagup\text{R} \\ \text{NH—C}\diagdown\text{R}' \end{array}$$

1. The Action of Alkaline Hypohalites on Disubstituted Cyanoacetamides[6] and Malonamides.[7]—Hydantoin itself was made by Weidel and Roithner[8] by the action of sodium hypobromite on malonamide, but in their experiments the yields were very small. This method, applicable to the synthesis of dialkyl as well as aryl-alkyl hydantoins with the substitutents both in the 4,4 position, is the subject of several patents, and appears to be the one most largely used commercially. The hypohalite in dil. alkaline solution is allowed to stand for some hours with the acid amide, followed by the application of heat for a short period. The reactions are

$$C_6H_5(C_2H_5)C(CN)CONH_2 \longrightarrow C_6H_5(C_2H_5)C(CONH_2)_2 \xrightarrow[\text{KOCl}]{}$$

$$C_6H_5(C_2H_5)C(CONH_2)NCO \longrightarrow \begin{array}{c} \text{NH—CO} \\ |\qquad | \\ \text{CO}\qquad | \\ |\qquad | \diagup C_6H_5 \\ \text{NH—C}\diagdown C_2H_5 \end{array}$$

[2] Fraenkel, "Arzneimittel Synthese," Julius Springer, Berlin, 1919, p. 476.

[3] May, "The Chemistry of Synthetic Drugs," Longmans, Green and Co., 1918, p. 57.

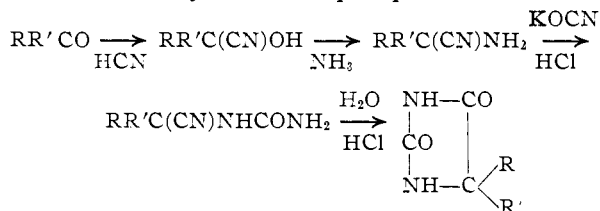[4] Loewe, *Deut. med. Wochschr.*, **38**, 947 (1912).

[5] Baum, *Therap. Monatsh.*, **33**, 385 (1919).

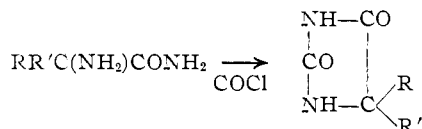[6] U. S. pat., 1,285,703 (1918); and Swiss pat., 72,561; 74,094 (1917).

[7] Ger. pat., 309,508; 310,426 (1919); and Swiss pat., 74,189; 74,190 (1917).

[8] Weidel and Roithner, *Monatsh.*, **17**, 172 (1896).

2. The Action of Alkali Cyanate on Disubstituted Amino-aceto-nitrile.[9]—The starting substance is a ketone, which is converted by prussic acid to the cyanohydrin. Ammonia reacts with the cyanohydrin to produce a disubstituted amino-acetonitrile. The aminonitrile is dissolved in hydrochloric acid, treated with alkali cyanate, and the solution boiled, which causes the hydantoin to precipitate.

$$RR'CO \xrightarrow[HCN]{} RR'C(CN)OH \xrightarrow[NH_3]{} RR'C(CN)NH_2 \xrightarrow[HCl]{KOCN}$$

$$RR'C(CN)NHCONH_2 \xrightarrow[HCl]{H_2O}$$

$$\begin{array}{l} NH-CO \\ | \qquad | \\ CO \qquad | \\ | \qquad R \\ NH-C\underset{R'}{\overset{R}{\diagup}} \end{array}$$

3. The Action of Phosgene on Disubstituted Amino-acetamide.[9]—In addition to phosgene, a variety of reagents such as oxalyl chloride, diphenyl carbonate, or chlorocarbonic ester[9] may be used to supply the additional carbon atom and close the ring. Carbon disulfide will function in the same way[10] producing a thiohydantoin, which is easily desulfurized.

$$RR'C(NH_2)CONH_2 \xrightarrow[COCl]{} \begin{array}{l} NH-CO \\ | \qquad | \\ CO \qquad | \\ | \qquad R \\ NH-C\underset{R'}{\overset{R}{\diagup}} \end{array}$$

The only work done on the first method was an attempt to convert ethyl phenylethyl-malonate, which is a readily available intermediate in the manufacture of phenylethyl-barbituric acid, by the action of ammonia into phenylethyl-malonamide. This did not succeed; the ammonium salt of phenylethyl-malonic acid was the only product which could be isolated when ammonia and the ester interacted for weeks, even when the mixture was thoroughly stirred at intervals. This confirms the experience of Meyer,[11] who has found it very difficult, and in many cases impossible to prepare acid amides from ethyl disubstituted malonates in the usual way. The only records in the patent literature indicate that the malonamides used in the hypohalite process were made from the corresponding cyano-acetamides either by the action of conc. sulfuric acid[12] or phosphorus pentachloride.[13]

This investigation is concerned primarily with the second method outlined above, which has been considerably modified. The first step to be considered is the formation of phenylethyl-amino-acetonitrile.

[9] Ger. pat., 310,427.
[10] *Centr.*, **1919**, [2] 423.
[11] Meyer, *Monatsh.*, **27**, 1083 (1906).
[12] Ger. pat., 309,508, 310,426 (1919).
[13] Swiss pat., 74,189 (1917).

In 1850 Strecker[14] prepared the nitrile of α-aminopropionic acid (alanine) by the action of prussic acid on aldehyde-ammonia. Thirty years later Tiemann[15] suggested a reversal of this operation, or in other words the action of prussic acid on aldehydes and ketones and the subsequent conversion of the cyanohydrin so formed to aminonitrile by the use of alcoholic ammonia. Ljubawin[16] pointed out that the two phases of the Strecker-Tiemann reaction may be combined and the whole operation carried out in one step by the use of ammonium cyanide as a reagent. Zelinsky[17] prefers to consider that ammonium cyanide is essentially the same in its action as if hydrocyanic acid and ammonia were allowed to act simultaneously upon the ketone or aldehyde carboxyl group. Gulewitsch and Wasmus[18] have made a very extensive study of the action of ammonium cyanide on a number of ketones of the aliphatic series, practically generalizing the reaction. Their yields varied from 42% to 88%. In continuation of this work Jawelow[19] has studied the action of ammonium cyanide on the ketones of the aliphatic aromatic series. The yields of the aminonitriles are considerably lower than those from purely aliphatic ketones, dropping to a range of 20% to 72%. Wiekmann[20] has proved that ammonium cyanide will not react with aromatic ketones.

In this investigation, it has been shown that the reaction of ammonium cyanide with phenylethyl ketone proceeds smoothly in absolute alcohol solution, and with satisfactory yield. The ammonium cyanide may be prepared as a solid by mixing hydrogen cyanide and ammonia, although it proved about as satisfactory and more convenient to make a solution of the reagent by mixing absolute alcohol and hydrocyanic acid and bubbling into the mixture dry ammonia in slight excess. No aminonitrile was formed when an aqueous solution of potassium cyanide and ammonium chloride was substituted for alcoholic ammonium cyanide. Likewise, no nitrile could be made in a dil. alcoholic solution of ammonium cyanide. Even with 95% alcohol the yield was extremely low. Neither excess of reagent nor the amount of the solvent appeared to have any effect on the yields. The reaction was carried out in all cases at room temperature, the time being from 1 to 4 days.

In no case was all the phenylethyl ketone reacted upon. However, all unchanged ketone was readily recovered by extraction of a solution of the aminonitrile hydrochloride with ether. Yields were calculated on the basis of the total ketone employed and on the basis of that which was actually used in the reaction, allowance being made for the recovered ketone. The maximum yield obtained was 55% on the first basis and 91% on the second. Since the recovered ketone is practically pure and may be used again without redistillation, it seems to be entirely proper to consider the yields in this reaction at the higher figure.

[14] Strecker, *Ann.*, **75**, 27 (1850).

[15] Tiemann, *Ber.*, **13**, 381 (1880).

[16] Ljubawin, *Centr.*, **1881**, 119; *J. Russ. Phys. Chem. Soc.*, **13**, 505 (1881).

[17] Zelinsky, *Ber.*, **39**, 1722 (1906).

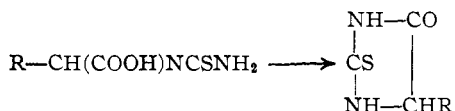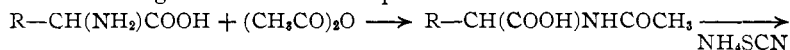[18] Gulewitsch and Wasmus, *ibid.*, **39**, 1181 (1906).

[19] Jawelow, *ibid.*, **39**, 1195 (1906).

[20] Wiekmann, *ibid.*, **39**, 1200 (1906).

While the addition of alkali cyanide to hydrochloric acid solution of phenylethyl-amino-acetonitrile, provided the solution is boiled, will produce 4,4-phenylethyl-hydantoin, the yields are low. Bailey and Read[21] have found that glacial acetic acid is an ideal solvent for reactions with cyanic acid, and that mixtures of acetic acid and other solvents are also quite satisfactory. Accordingly, acetic acid has been used in this investigation in the preparation of phenylethyl-hydantoin. The intermediate phenylethyl-hydantoic-nitrile was isolated, purified, and subsequently converted to the hydantoin by boiling it with hydrochloric acid. The yield of phenylethyl-hydantoin from phenylethyl-amino-acetonitrile, when hydrochloric acid was used, was about 30%, and when glacial acetic acid was used the yield was more than double this value.

It was found possible to pass from phenylethyl ketone to phenylethyl-hydantoin without isolating intermediate products. The yield in this case, allowing for recovered ketone, was about 62% of that calculated.

Johnson[22] has prepared several 2-thiohydantoins. The acetyl derivative of an amino acid first prepared was treated with ammonium or potassium thiocyanate, and the thiohydantoic acid formed in this way was boiled with hydrochloric acid. The entire operation can be carried out without isolating the intermediate products.

$$R{-}CH(NH_2)COOH + (CH_3CO)_2O \longrightarrow R{-}CH(COOH)NHCOCH_3 \xrightarrow[NH_4SCN]{}$$

$$R{-}CH(COOH)NCSNH_2 \longrightarrow \begin{array}{c} NH{-}CO \\ | \quad\quad | \\ CS \quad\quad | \\ | \quad\quad | \\ NH{-}CHR \end{array}$$

Since thiohydantoins are easily desulfurized, this appeared to be a commercial possibility for the production of 4,4-phenylethyl-hydantoin, especially in view of the relatively small cost of ammonium thiocyanate as compared with potassium cyanate. However, no reaction was observed between the acetyl derivative of phenylethyl-amino-acetic acid, C_6H_5-$(C_2H_5)C(NHCOCH_3)COOH$, and either ammonium or potassium thiocyanate with conditions the same as those employed by Johnson. Likewise, the acetyl derivative of phenylethyl-amino-acetonitrile will not react with thiocyanates. As this is probably the first observed instance of a failure of an α-amino acid to respond to this characteristic reaction, further investigation will be made as to the effect of various substitutents in the α-position of the acid. Whether we are dealing here with a case of steric hindrance remains to be established.

Experimental Part

Action of Ammonia on Diethyl Phenylethyl-malonate.—Sixty g. of the malonic ester was allowed to stand for 6 weeks with a fairly concentrated aqueous solution of am-

[21] Bailey and Read, THIS JOURNAL, **37**, 1884 (1915).

[22] Johnson, *ibid.*, **35**, 780 (1913).

monia. The mixture was shaken at intervals and then vigorously stirred for 20 hours. A small amount of solid separated. Crystallized from water, it separated in thin leaflets and melted at 154–155°. Analysis indicated that it was the ammonium salt of phenyl-ethyl-malonic acid.

Analysis. Calc. for $C_{11}H_{14}O_2N_2$: N, 13.6. Calc. for $C_{11}H_{18}O_4N_2$: N, 11.6. Found: 11.8.

Preparation of Propionyl Chloride, C_6H_5COCl.—Propionyl chloride

was prepared not only by the usual methods with phosphorus trichloride or phosphorus pentachloride, but also by the chlorination of propionic acid in the cold with sulfur monochloride present.

To 540 g. of propionic acid 245 g. of sulfur monochloride was added and chlorine was passed through the mixture while it was stirred for 15 hours. The chlorination proved to be incomplete at this point, since 150 g. of unchanged propionic acid was recovered. There was also considerable sulfur monochloride, which was removed from the propionyl chloride by treatment with hydrogen sulfide. The propionyl chloride obtained amounted to 250 g. This product functioned as satisfactorily in the subsequent preparation of phenylethyl ketone as that prepared by the phosphorus halide methods.[23]

Preparation of Phenylethyl Ketone, $C_6H_5COC_2H_5$.—Phenylethyl

ketone was made by Pampel and Schmidt[24] in 1886 by application of the Friedel and Crafts reaction. These investigators state that their yields were good, but give no data. In our preparation it was found necessary to employ vigorous mechanical stirring, and to keep the temperature of the reaction mixture below 20° until all reagents were added. Where occasional shaking was depended upon, the yields amounted on an average to 40% but, with the above precautions, yields were more than doubled. The following preparation is given as typical of the final procedure.

Two hundred g. of finely divided anhydrous aluminum chloride was suspended in 300 g. of dry benzene in a flask equipped so that the mixture could be thoroughly stirred and cooled. A mixture of 126 g. of propionyl chloride and 105 g. of benzene was run in drop by drop, the entire time of addition being 3 hours. At the end of this time the reaction mixture was kept for 2 hours at 50°. The contents of the flask were cooled and poured over crushed ice; and, after 50 cc. of conc. hydrochloric acid had been added, the phenylethyl ketone and benzene were removed by distillation with steam. Thus, 152 g. of phenylethyl ketone was obtained. It boiled between 200° and 220°; yield, 84%.

Preparation of Ammonium Cyanide.—Solid ammonium cyanide was

prepared first by the action of dry ammonia gas on hydrogen cyanide. Since this method presents a mechanical difficulty, in that the tubes through

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[23] This experiment was carried out purely to ascertain whether propionyl chloride could be made by this method. Auger and Behal [*Bull. soc. chim.*, [3] **2**, 144 (1889)] have shown this to be an excellent process for making acetyl chloride. The author has been able to prepare chloro-acetyl chloride from chloro-acetic acid in 95% yield by this method. In order to obtain good results, it is necessary to use an efficient chlorine distributor such as a "Filtros" block, and to employ the acid in slight excess above the 0.25 mol of sulfur monochloride. The last named precaution avoids the necessity for the removal of sulfur chloride.

[24] Pampel and Schmidt, *Ber.*, **19**, 2896 (1886).

which the gases are passed become stopped, it was found more convenient to prepare this reagent in absolute alcohol solution. For this purpose absolute hydrogen cyanide was dissolved in alcohol, and dry ammonia gas in slight excess was bubbled through the solution.

Phenylethyl-amino-acetonitrile Hydrochloride, $C_6H_5(C_2H_5)C(CN)$-$NH_2.HCl$.—After a large number of experiments had been performed to determine the optimum conditions for the reaction between ammonium cyanide and phenylethyl ketone, the best result was obtained by the following method.

Twenty g. of ammonium cyanide, made by the action of dry ammonia on absolute hydrogen cyanide, was mixed with 50 g. phenylethyl ketone, and to this paste 25 cc. of absolute alcohol was added. After this solution had stood at room temperature for 3 days the product was poured into dil. hydrochloric acid, while the solution was cooled. The oil, which was separated by extraction with ether, was dried over calcium chloride and the ether was distilled. In this way 22 g. of unchanged ketone was recovered. The aqueous portion was made alkaline with ammonia, the phenylethyl-amino-aceto-nitrile, which appears as a yellow oil, was extracted with ether, and the ether extract dried over calcium chloride. When the ethereal solution was saturated with dry hydrogen chloride, the hydrochloride of phenylethyl-amino-acetonitrile separated. Dried over caustic soda, this weighed 37 g. and proved to be pure, melting at 119°. The yield, allowing for the recovered ketone, was 90%.

The following experiments were carried out to show the possibilities of using a solution of ammonium cyanide rather than the dry salt.

1. A 1.5 N ammonium hydroxide solution amounting to 275 cc. was treated with hydrogen cyanide prepared from 20 g. of potassium cyanide. To this aqueous solution of ammonium cyanide 25 g. of phenylethyl ketone was added, and the reaction mixture, which stood for 2 days, was shaken frequently. From this, 21 g. of phenylethyl ketone was recovered unchanged and only 0.5 g. of the hydrochloride of phenylethyl-amino-acetonitrile was isolated.

2. The above experiment was repeated with a slight modification. Just enough alcohol was added to dissolve the phenylethyl ketone, the final composition of the solvent being about 45% alcohol by volume. No aminonitrile hydrochloride could be isolated.

3. In a third experiment 95% alcohol was treated with ammonia gas until the solution was of 1.4 N concentration. Hydrogen cyanide prepared from 20 g. of potassium cyanide was bubbled into this solution. After standing for 1 day, 18 g. of unchanged ketone was recovered and 2.1 g. of the hydrochloride of phenylethyl-amino-acetonitrile obtained. This amounts to a 20% yield, allowing for recovered ketone, but less than 30% of the ketone reacted.

4. In another experiment 170 cc. of 3.84 N alcoholic ammonia, made with absolute alcohol, was treated with an excess of the hydrocyanic acid obtained from 60 g. of sodium cyanide. To this solution 50 g. of phenylethyl ketone was added and the material was allowed to stand for 4 days. The recovered ketone amounted to 60% of the total used, and the yield of aminonitrile hydrochloride, on the basis of the remaining 40%, was 57%. Polymerization products from the hydrocyanic acid caused considerable difficulty, since they interfered with the isolation of the hydrochloride.

5. In still another experiment 200 cc. of absolute alcohol was treated with dry ammonia until the concentration was 4.4 N. To this solution 100 g. of phenylethyl ketone was added, and anhydrous hydrogen cyanide from 50 g. of sodium cyanide

was distilled into the mixture. After 2 days, 60 g. of ketone was recovered and 37 g. of the hydrochloride of phenylethyl-amino-acetonitrile was obtained; yield, 63%.

6. In the direct preparation of phenylethyl-hydantoin described later in this article, the procedure used was as follows. Phenylethyl ketone and anhydrous hydrogen cyanide were mixed and dissolved in absolute alcohol. This solution was treated with dry ammonia in slight excess and the reaction mixture allowed to stand for 1 day. Phenylethyl-amino-acetonitrile was not isolated as such but, after the removal of the unchanged ketone, it was converted directly to phenylethyl-hydantoin. On the basis of the preparation of the hydantoin from the aminonitrile, in which the yields were quite constant, the calculated yield by this procedure was 90%.

Summing up these results, phenylethyl ketone will not react with ammonium cyanide in aqueous solution or in dil. alcoholic solution. The yields are poor in 95% alcoholic solution. Reasonably good results were obtained when an absolute alcohol solution of ammonium cyanide made by the action of ammonia on hydrogen cyanide in alcohol was employed. The best results were obtained when dry ammonium cyanide dissolved in a small amount of alcohol was allowed to react with phenylethyl ketone, and when a mixture of hydrogen cyanide and phenylethyl ketone was dissolved in alcohol and treated with ammonia.

Nitrile of Phenylethyl-hydantoic Acid, $C_6H_5(C_2H_5)C(NHCONH_2)CN$.—
Five g. of the hydrochloride of phenylethyl-amino-acetonitrile was dissolved in 30 cc. of glacial acetic acid and to this solution powdered potassium cyanate, 2 g. in all, was added slowly in small portions. After the reaction mixture had been warmed for an hour at 60°, it was poured into 5 times its volume of cold water. The crystalline solid so obtained amounted to 4 g. It is very slightly soluble in cold water, somewhat more soluble in hot water, and fairly soluble in alcohol and in glacial acetic acid. It is insoluble in cold dil. caustic soda. It melts without decomposition at 201° to a clear liquid. Crystallized from water, it separates in the form of long, colorless needles.

Analysis. Calc. for $C_{11}H_{13}ON_3$: N, 20.7. Found: 20.9.

A series of experiments to determine optimum conditions showed that the yield was only slightly lowered when a mixture of acetic acid and alcohol or even 50% acetic acid was substituted for glacial acetic acid. It was further shown that at 60° the yield is increased only a small amount above that obtained at room temperature. It is not necessary to isolate the hydrochloride for this preparation, since the crude phenylethyl-amino-acetonitrile may be used directly. The yields in this process averaged between 75% and 80% according to conditions.

4,4-Phenylethyl-hydantoin.—When 7.6 g. of the nitrile of phenylethyl-hydantoic acid mixed with 50 cc. of 20% hydrochloric acid was heated for 1 hour on the steam-bath, the nitrile dissolved completely. In a few minutes there appeared a crystalline solid, which increased in amount until the liquid had changed to a thin paste. The hydantoin obtained by this method weighed 6.5 g., an 85% yield. It was recrystallized twice from water.

Calc. for $C_{11}H_{12}O_2N_2$: N, 13.7. Found: N, 13.8.

The hydantoin melts to a clear liquid without decomposition at 199°. It is sparingly soluble even in hot water, extremely insoluble in cold water, but fairly soluble in alcohol. It dissolves quite readily in dil.

sodium hydroxide from which it is precipitated by addition of an excess of mineral acid.

When the hydantoin is made without isolation of the nitrile by the use of hydrochloric acid, much lower yields resulted.

Ten g. of phenylethyl-amino-acetonitrile hydrochloride was dissolved in 50 cc. of water, and 4.5 g. of potassium cyanate dissolved in 25 cc. of water was added; 35 cc. of conc. hydrochloric acid was poured into the reaction mixture after it had been allowed to stand for an hour, and the solution was boiled for another hour. Crystals separated from the boiling solution. After a day, 3.2 g. of hydantoin was obtained; yield, 30%.

The yield of hydantoin from the hydrochloride of phenylethyl-amino-acetonitrile or from the free nitrile averaged from 60% to 68% of calculated value when glacial acetic acid was used as the solvent for cyanic acid.

The following preparation of the hydantoin from phenylethyl ketone, which was carried out without isolation of intermediate products represents the most convenient method of procedure for making the hydantoin in quantities.

Twenty-five g. of phenylethyl ketone was mixed with absolute hydrocyanic acid prepared from 50 g. of sodium cyanide, and 150 cc. of absolute alcohol was added. Dry ammonia was bubbled through this solution until no further absorption was noted After standing for 1 day, this solution was poured into dil. hydrochloric acid and the unchanged ketone was extracted with ether. This amounted to 10 g. The aqueous portion was made alkaline with ammonia. The oil which separated was extracted with ether, dried over calcium chloride, and the ether removed by application of a gentle heat. The crude phenylethyl-amino-acetonitrile was dissolved in glacial acetic acid, and to this was added 12 g. of potassium cyanate. After the reaction mixture had been warmed for an hour it was poured into water, the hydantoic nitrile was collected on a filter, and finally boiled with 150 cc. of 20% hydrochloric acid. From this product there was obtained a total of 14.1 g. of hydantoin, a yield of 62% of that theoretically possible from the ketone, when allowance is made for the recovered reagent. On the basis of other experiments, the yield of phenylethyl-amino-acetonitrile was calculated at 90%.

Attempt to Prepare 4,4-Phenylethyl-2-thiohydantoin.—Five g. of the hydrochloride of phenylethyl-amino-acetonitrile was converted to the free nitrile by dissolving it in water, neutralizing the hydrochloric acid with ammonia and extracting the nitrile with ether. After drying the ether extract over calcium chloride and gently warming it to remove the ether, the nitrile was placed in 25 cc. of acetic anhydride, treated with 2.5 g. of potassium thiocyanate, and the solution warmed gently for 1 hour. The resulting clear orange-colored liquid was poured into 150 cc. of cold water. An oil immediately separated which changed to a light yellow solid weighing 3.2 g. Recrystallized from water, this proved to be the acetyl derivative of phenylethyl-amino-acetonitrile described below.

Phenylethyl-acetylamino-acetonitrile, $C_6H_5(C_2H_5)C(NHCOCH_3)CN$.—Fifteen g. of phenylethyl-amino-acetonitrile was poured into 50 cc. of acetic anhydride and the solution was warmed for one hour on a steam-plate. When this material was poured into water, an oil formed which changed to a white solid with a very slightly yellowish tint. Recrystallized from alcohol or water, the substance melts undecomposed at 147°.

Analysis. Calc. for $C_{12}H_{14}ON_2$: N, 13.9. Found: 13.6.

Phenylethyl-acetylamino-acetic Acid, $C_6H_5(C_2H_5)C(NHCOCH_3)COOH$.—Four g. of phenylethyl-acetyl-amino-acetonitrile was dissolved in dil. hydrochloric acid and the solution was evaporated slowly to dryness on a steam-plate. The solid residue was taken

up in water and a white solid was collected which weighed 2.7 g.   Recrystallized from water or alcohol, this material melted at 225° with gas evolution and decomposition.

Analysis.   Calc. for $C_{12}H_{15}O_3N$:   N, 6.3.   Found: 6.3.

This acid gave no indication of reaction with either potassium or sodium thiocyanate. Four g. of phenylethyl-acetylamino-acetic acid and 3 g. of potassium thiocyanate were dissolved in a mixture of 18 cc. of acetic anhydride and 2 cc. of glacial acetic acid, and the solution was warmed for 1 hour on a steam-plate.   When it was poured into 200 cc. of cold water, an oil separated which solidified later.   Recrystallized from alcohol this solid melted at 225° with gas evolution and decomposition.   Mixed with an equal quantity of the original phenylethyl-acetylamino-acetic acid and recrystallized from alcohol, the melting point remained constant at 225°.

Summary

The purpose of this investigation was the preparation of 4,4-phenylethyl-hydantoin.   The following observations have been made.

1. Phenylethyl ketone reacts with an absolute alcohol solution of ammonium cyanide to form phenylethyl-amino-acetonitrile.   Under the best conditions the yield is 90%.

2. The above reaction will not take place in aqueous solution, and even in 95% alcohol the yields are very low.

3. Phenylethyl-amino-acetonitrile reacts with potassium cyanate in glacial acetic acid to form the nitrile of phenylethyl-hydantoic acid in 80% yield.   When this compound is boiled with 20% hydrochloric acid it is converted into 4,4-phenylethyl-hydantoin in 85% yield.

4. It is possible to prepare 4,4-phenylethyl-hydantoin by the procedure outlined above from phenylethyl ketone without isolating and purifying intermediate products; yield 62%.

5. Potassium or ammonium thiocyanate will not react with phenylethyl-amino-acetonitrile in glacial acetic acid.

6. Neither phenylethyl-acetylamino-acetic acid nor its nitrile will react with potassium thiocyanate in acetic anhydride solution.

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