Dibromo Benzoylmesitoylmethane (XII).—A solution of 20 g. of concd. sulfuric in 40 cc. of glacial acetic acid was added with cooling to a solution of 16 g. of pyridine in 40 cc. glacial acetic acid. To this mixture was added 26.8 g. of enol (IX) dissolved in 170 cc. of glacial acetic acid. Finally with cooling and vigorous shaking, 32 g. of bromine in 400 cc. of acetic acid was added. The bromine was taken up rapidly. The acetic acid was distilled under diminished pressure; the residual oil was poured into water and extracted with ether. The ethereal solution was washed with sodium bicarbonate solution and with water. The ether was evaporated and the resulting pale yellow oil crystallized from methyl alcohol yielding pale yellow crystals, melting at 101–106°. Recrystallization from low-boiling petroleum gave 16 g. of pale yellow crystals melting at 107–108°.

Anal. Calcd. for $C_{18}H_{16}O_2Br_2$: C, 50.9; H, 3.8; Br, 37.7. Found: C, 51.0; H, 3.9; Br, 37.8.

This dibromide upon treatment with glacial acetic acid and potassium acetate is converted into mesityl phenyl diketone, identified by comparison with an authentic sample.

The Acetate (XIV).—Five grams of the bromobenzoylmesitoylmethane was refluxed for one hour with an excess of acetyl chloride. The acetyl chloride was pumped off and the residue crystallized from methyl alcohol. A practically quantitative yield of colorless crystalline solid, melting at 96°, was obtained.

Anal. Calcd. for $C_{20}H_{19}O_3Br$: C, 62.0; H, 4.9. Found: C, 62.0; H, 5.2.

This substance is non-enolic and is hydrolyzed by acids to the parent bromo compound. It is not acetylated further by potassium acetate in acetic anhydride, nor is it reduced by potassium iodide in acid solution. The same compound is obtained when the bromobenzoylmesitoylmethane is treated with acetic anhydride.

The Action of Acetic Anhydride–Potassium Acetate on Bromobenzoylmesitoylmethane (XIV) and (XV).—To a hot mixture of 10 g. of freshly fused potassium acetate and 50 cc. of acetic anhydride were added 10 g. of the monobromo compound. This mixture was refluxed gently for forty-five minutes. The solution turned dark brown and potassium bromide separated out. When cold it was poured into a large volume of cold water and stirred vigorously until the acetic anhydride was decomposed. It was then taken up in ether, washed with sodium bicarbonate solution, and finally with water, dried and evaporated. The residue was dissolved in methyl alcohol, from which by fractional crystallization 5 g. of the bromo acetate, melting at 96°, and 1.0 g. of the diacetate, melting at 131°, were obtained. Both products were identified by their mixed-melting points with known samples.

Summary

In this paper we have reported the properties of the enolic modification of benzoylmesitoylmethane, which properties are influenced considerably by the presence of the mesityl nucleus, which seems not only to activate the *alpha* substituents but also to have a directing influence upon enolization.

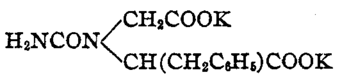
WASHINGTON, D. C. RECEIVED FEBRUARY 12, 1940

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF MOUNT HOLYOKE COLLEGE]

Ring Closure of Acylic Ureides Resulting from the Elimination of Alcohol: A Study of the Esters of beta-Phenylalanine-N-acetic Acid and Related Compounds[1]

BY DOROTHY A. HAHN, MARGARET J. MCLEAN AND MARGARET M. ENDICOTT

Further study of the derivatives of β-phenylalanine-N-acetic acid has resulted in the synthesis of the isomer of C-5-benzylhydantoin-N-1-acetate, to which reference was made in an earlier report.[1a] It was then stated that although the formation of two isomeric hydantoin-acids was theoretically possible following the hydrolysis of the ureidic salt

(I) 

$$\mathrm{H_2NCON}\begin{matrix}\diagup\mathrm{CH_2COOK}\\ \diagdown\mathrm{CH(CH_2C_6H_5)COOK}\end{matrix}$$

under the action of hydrochloric acid, ring closure actually had been observed to take place in one sense only.[2] Moreover, since the product[3]

(II) $\mathrm{HOOCCH_2NCONHCOCHCH_2C_6H_5}$

was precipitated instantly in yields averaging more than 90% of the theoretical, it seemed reasonable to conclude that the rates at which the two carboxyl groups were capable of reacting respectively with the hydrogen of the amide group in the ureide must differ greatly in magnitude. It appeared probable therefore that the formation of the isomer

(III) $\mathrm{HOOC(CH_2C_6H_5)CHNCONHCOCH_2}$

could not be expected under ordinary conditions. However, it was still possible that in the case of a compound having the configuration

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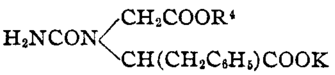
[1] Original manuscript received November 7, 1939.

[1a] Hahn and Endicott, THIS JOURNAL, **60**, 1045 (1938).

[2] A similar observation has been reported by E. Ware, *ibid.*, **60**, 2653 (1938), who found that although two isomeric hydantoins were theoretically possible as a result of the cyclization of a hydantoic derivative of tyrosine-N-acetic acid, only one product could be isolated and identified, namely, $\mathrm{HOOCCH_2NCON(C_6H_5)COCHCH_2\text{-}C_6H_4OH}$.

[3] The configuration of this compound has been definitely established, Hahn and Endicott, *loc. cit.*, p. 1042.

(IV)

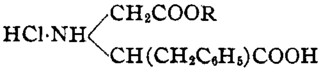


$$\mathrm{H_2NCON}\left\langle\begin{array}{l}\mathrm{CH_2COOR}^4\\ \mathrm{CH(CH_2C_6H_5)COOK}\end{array}\right.$$

ring closure, taking place in an alkaline medium and accompanied by the elimination of alcohol, might occur. This possibility has been realized and it can now be stated that cyclization of this type has been effected following the synthesis of certain derivatives of β-phenylalanine-N-acetic acid, a brief discussion of which follows.

The mono-alkyl esters of this unsymmetrical acid, together with the corresponding hydrochlorides, may be assumed to be capable of existing in two isomeric modifications, such as, for example

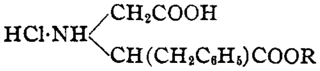
(a)



$$\mathrm{HCl{\cdot}NH}\left\langle\begin{array}{l}\mathrm{CH_2COOR}\\ \mathrm{CH(CH_2C_6H_5)COOH}\end{array}\right.$$

and

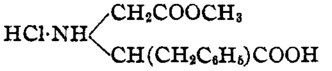
(b)



$$\mathrm{HCl{\cdot}NH}\left\langle\begin{array}{l}\mathrm{CH_2COOH}\\ \mathrm{CH(CH_2C_6H_5)COOR}\end{array}\right.$$

It has been found, however, that only *one* salt of this type can be isolated as a result of dissolving the imino acid in a hydrogen chloride solution of either methyl or ethyl alcohol. For reasons to be discussed later these products, which under very specific conditions were precipitated in almost pure condition and in yields averaging 70% of the theoretical, were assumed to possess the configurations

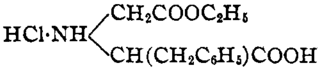
(V)



$$\mathrm{HCl{\cdot}NH}\left\langle\begin{array}{l}\mathrm{CH_2COOCH_3}\\ \mathrm{CH(CH_2C_6H_5)COOH}\end{array}\right.$$

and

(VI)

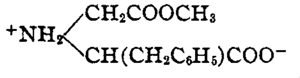


$$\mathrm{HCl{\cdot}NH}\left\langle\begin{array}{l}\mathrm{CH_2COOC_2H_5}\\ \mathrm{CH(CH_2C_6H_5)COOH}\end{array}\right.$$

The filtrate contained a mixture of the hydrochlorides of the free acid, its mono- and di-alkyl esters.[5]

Following their final purification, both salts were transformed (under loss of hydrogen chloride) into the corresponding free esters:

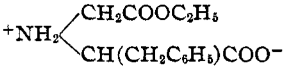
(VII)



$$^{+}\mathrm{NH_2}\left\langle\begin{array}{l}\mathrm{CH_2COOCH_3}\\ \mathrm{CH(CH_2C_6H_5)COO^-}\end{array}\right.$$

and

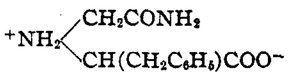
(VIII)[6]



$$^{+}\mathrm{NH_2}\left\langle\begin{array}{l}\mathrm{CH_2COOC_2H_5}\\ \mathrm{CH(CH_2C_6H_5)COO^-}\end{array}\right.$$

These compounds are almost insoluble in water, alcohol and other organic solvents but both dissolve readily in ammoniacal solutions of alcohol to form one and the same monamide

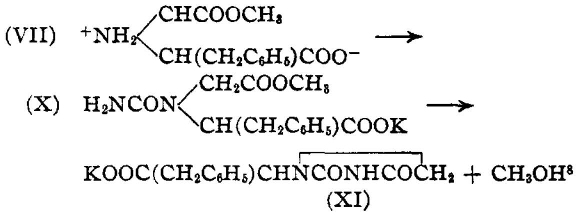
(IX)



$$^{+}\mathrm{NH_2}\left\langle\begin{array}{l}\mathrm{CH_2CONH_2}\\ \mathrm{CH(CH_2C_6H_5)COO^-}\end{array}\right.$$

From this it follows that both esters possess the same configuration.[7]

The formulas that have been assigned to the compounds V, VI, VII and VIII, irrespective of their close chemical interrelationships, depend upon the fact that under the action of aqueous potassium cyanate *all four* were transformed into acyclic ureides which in weakly alkaline media underwent ring closure to give one and the same final product, XI. In the case of the compound VII, for example, the course of this reaction may be indicated most simply as



$$\text{(VII)}\quad {}^{+}\mathrm{NH_2}\left\langle\begin{array}{l}\mathrm{CHCOOCH_3}\\ \mathrm{CH(CH_2C_6H_5)COO^-}\end{array}\right. \longrightarrow$$

$$\text{(X)}\quad \mathrm{H_2NCON}\left\langle\begin{array}{l}\mathrm{CH_2COOCH_3}\\ \mathrm{CH(CH_2C_6H_5)COOK}\end{array}\right. \longrightarrow$$

$$\mathrm{KOOC(CH_2C_6H_5)CH\overline{NCONHCOC}H_2} + \mathrm{CH_3OH}^8$$

(XI)

The presence in the reaction mixture of a compound having the configuration XI was assumed from the fact that addition of hydrochloric acid resulted in the formation of an hydantoin acid, which on analysis was found to be isomeric with II.[3] While the formula which has been assigned to this new compound III has not as yet been confirmed as the result of a second synthesis, it is supported by a consideration of the following facts. The acids II and III show a striking similarity in their physical and chemical properties. For example, a comparison of their absorption curves reveals a very close relationship, since both show selective absorption that is identical

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(4) Whenever used, R may be understood to denote either a methyl or an ethyl group.

(5) That this filtrate contained no decomposition products was shown by the fact that when evaporated to dryness and the residue treated as described by Hahn and Endicott (*loc. cit.*, p. 1041, footnote 4), the free imino-acid was regenerated in amounts corresponding very closely to the theoretical. Reference will be made frequently to this as a general procedure for recovering the free imino-acid.

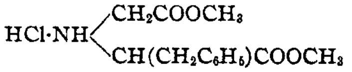
(6) It may be noted that in the case of imino-diacetic acid only a single compound of this type was isolated. This was referred to by Jongkees [*Rec. trav. chim.*, **27**, 297 (1908)] as an "ether-salt," $\mathrm{NH(CH_2COOC_2H_5)CH_2COOH}$, in which the function of the acid neutralizes that of the secondary amine since the compound is almost neutral to turmeric. It seems curious that the corresponding methyl ester was never separated, but this may be due to the fact that, as in the case of the corresponding derivatives of beta-phenylalanine-N-acetic acid, it was more difficult to prepare. For example, while the hydrochloride V is extremely stable in aqueous solution, VI is partially hydrolyzed even at ordinary temperatures and when the dry salt was treated with boiling water, its solution was followed almost instantly by the precipitation of VIII.

(7) A comparison of the electrolytic dissociation constants of VII, VIII and IX has revealed, moreover, that all three behave like weak monobasic acids. These constants agree very closely and are of the order of 10^{-7} (McLean, unpublished work).

(8) Ring closures accompanied by the elimination of alcohol which resulted in the formation of both hydantoin and hydantoin-N-1-acetic acid, have been reported by J. R. Bailey, *Am. Chem. J.*, **28**, 393 (1902), and by Bailey and Snyder, THIS JOURNAL, **37**, 945 (1915).

up to 37000 cm.$^{-1}$. Differences are to be found only in the intensities of absorption characteristic of the phenyl group and these may be accounted for as due to differences in the relative positions of this group in the two molecules.[9] Both acids have been shown to be dibasic as a result of electrometric titrations,[10] although due to a weakly acidic hydrogen atom in the N-3-position, each yields respectively only a single stable mono-sodium salt. The corresponding methyl esters also have been prepared and found to be isomeric and not identical. It may be added that the acid III has been obtained in yields of 70% from each of the compounds designated as V, VI, VII and VIII and that the course of the reaction in the case of VII has been demonstrated by the fact that methyl C-5-benzylhydantoin-N-1-acetate,[11] which could be formed only as a result of ring closure of X under the action of hydrochloric acid, was actually isolated from the reaction mixture.

In conclusion it may be stated that only one dialkyl ester of β-phenylalanine-N-acetic acid has as yet been prepared and that this was separated in pure condition only in the form of its hydrochloride

(XII)[12] 

$$HCl\cdot NH\begin{cases}CH_2COOCH_3\\ CH(CH_2C_6H_5)COOCH_3\end{cases}$$

It is interesting to note that when this salt was treated with potassium cyanate and the reaction product subsequently hydrolyzed, both of the hydantoin-acids II and III were again isolated.

Experimental

The β-phenylalanine-N-acetic acid used in these experiments was prepared by alkaline hydrolysis of ethyl N-3-methyl-C-5-benzylhydantoin-N-1-acetate[13] and was purified by recrystallization from boiling water.

The hydrochloride of the mono-methyl ester, V, $HCl\cdot NH(CH_2COOCH_3)CH(CH_2C_6H_5)COOH$, m. p. 185–186° (dec.), was obtained in yields averaging 70 to 75% by dissolving the free acid in methyl alcohol under the action of hydrogen chloride. For example, to a clear solution of 5 g. of the free acid in 15 cc. of absolute methyl alcohol one-third saturated with dry hydrogen chloride,[14] after standing thirty minutes at 0° and then forty-eight hours at room temperature, 50 cc. of absolute ether was added.[15] After two hours the resulting white crystals were washed with a mixture of alcohol and ether (1:10)[16] and dried; weight 4.43 g.; m. p. 183–186°. On recrystallization from boiling acetone they decomposed sharply at 185–186°.

Anal. Calcd. for $C_{12}H_{15}O_4N\cdot HCl$: C, 52.65; H, 5.87; N, 5.12; Cl, 12.96. Found: C, 52.90; H, 5.85; N, 5.09; Cl, 12.79.

The salt is soluble in cold absolute methyl alcohol (1 g. in less than 3 cc.) and in acetone (1 g. in 500 cc. boiling and in 1250 cc. at 20°) but insoluble in ether. It loses hydrochloric acid readily to form the free ester VII when treated with the calculated quantity of dilute alkali but is stable in aqueous[17] and alcohol solutions. It yields the corresponding salt of the imino acid when warmed with concentrated hydrochloric acid,[18] and sodium and potassium salts on alkaline hydrolysis.[18]

The hydrochloride of dimethyl-β-phenylalanine-N-acetate, XII, $HCl\cdot NH(CH_2COOCH_3)CH(CH_2C_6H_5)COOCH_3$, m. p. 144–145° (dec.), was obtained in 70% yields from the hydrochloride of the imino acid after five days[19] of alternate saturation of a concentrated absolute methyl alcohol solution (8.5 g. in 25 cc.) with dry hydrogen chloride at 0°, and refluxing over a steam-bath. The clear solution evaporated to dryness under air blast gave a red gum which when dissolved in boiling acetone deposited white crystals; weight 6.8 g.; m. p. 138–142°. Recrystallized from acetone they decomposed sharply at 144–145°.[20]

Anal. Calcd. for $C_{13}H_{17}O_4N\cdot HCl$: C, 54.26; H, 6.30; N, 4.87; Cl, 12.32. Found: C, 54.20; H, 6.23; N, 4.70; Cl, 12.33.

The salt is very soluble in cold absolute methyl alcohol and moderately in acetone (1 g. in 75 cc. boiling and in 190 cc. at 20°)[21] but insoluble in ether. It separates from alcohol solutions on addition of ether in long, silk-like,

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[9] McLean, unpublished work.

[10] Their respective pK_1 and pK_2 dissociations are II, 2.81 and 8.96; III, 2.91 and 9.20. Compare Pickett and McLean, THIS JOURNAL, **61**, 423 (1939).

[11] The identity of this ester was confirmed by a mixed melting point with an analyzed specimen previously synthesized. Compare Hahn and Endicott, *loc. cit.*, p. 1044.

[12] The hydrochloride of the corresponding diethyl ester and the corresponding derivative of iminodiacetic acid could not be isolated, although Jongkees (*loc. cit.*, p. 296) finally obtained a small quantity of a crystalline compound to which he assigned the formula $HCl\cdot NH(CH_2COOC_2H_5)_2\cdot H_2O$.

[13] Hahn and Endicott, *loc. cit.*, 1042; also compare Hahn and Litzinger, *ibid.*, **54**, 4663 (1932), and Litzinger, *ibid.*, **56**, 676 (1934).

[14] Yields were lower and extremely variable when hydrogen chloride was passed directly into a suspension of the free acid in alcohol.

[15] Excess ether caused the precipitation of an oil.

[16] The filtrate on evaporation under air blast gave a gum from which hydrochlorides of the imino acid and of its mono- and di-methyl esters were separated, but which when warmed with dilute hydrochloric acid was completely transformed into the free imino acid.[5] A similar gum was obtained when an alcohol solution of the hydrochloride of the imino acid was evaporated to dryness.

[17] The salt is very soluble in cold water, from which it separates undecomposed but dilute solutions (10 g. in 100 cc.) after prolonged boiling (twelve hours) deposit a gum (0.3 g.) on cooling. This consists of a mixture of the free ester and its hydrochloride.

[18] Identification effected by comparison with analyzed specimens, Hahn and Endicott, *loc. cit.*, p. 1043.

[19] When action was stopped after four or five hours, a mixture was obtained from which less than 40% of the above salt could be separated. Compare Jongkees, *loc. cit.*, pp. 295–296.

[20] The same salt was obtained from oils or gums similar to those described in footnote 16. Separation was effected by dissolving the gum in water, and extracting with ether following additions of sodium bicarbonate. The ether solution when *perfectly dry* and saturated with hydrogen chloride, deposited the salt in form of a gum which on stirring changed into white crystals, m. p. 144–145°.

[21] Due to marked differences in their solubilities in acetone, mixtures consisting *exclusively* of the hydrochlorides of the mono- and di-methyl esters may be separated readily.

glistening white needles that form in rosettes. Warmed with dilute hydrochloric acid it gave the free acid.[5]

The hydrochloride of the mono-ethyl ester of β-phenylalanine-N-acetic acid, VI, $HCl \cdot NH(CH_2COOC_2H_5)CH(CH_2C_6H_5)COOH$, m. p. 170–172° (dec.), was obtained from the free acid in yields of 70–75%, when absolute ethyl alcohol was substituted for methyl in the corresponding experiment, V. The product, consisting of hard white crystals,[22] was recrystallized from boiling acetone.

Anal. Calcd. for $C_{13}H_{17}O_4N \cdot HCl$: C, 54.26; H, 6.30; N, 4.87; Cl, 12.32. Found: C, 54.50; H, 6.34; N, 4.84; Cl, 12.25.

The salt is very soluble in cold absolute ethyl alcohol but only slightly in acetone (1 g. in 300 cc. boiling and in 750 cc. at 20°) and insoluble in ether. It differs in its reactions from the corresponding methyl derivative only in that it loses its hydrochloric acid when dissolved in water.[23]

The free mono-methyl ester of β-phenylalanine-N-acetic acid, VII, $^+NH_2(CH_2COOCH_3)CH(CH_2C_6H_5)COO^-$, m. p. 208–210° (dec.), was obtained from the corresponding hydrochloride by adding at 0° an equivalent of (a) sodium methoxide to its methyl alcohol solution, or (b) potassium bicarbonate to an aqueous solution. The gelatinous precipitate, consisting of salt mixed with free ester which formed in both cases, was resolved into fine white crystals on stirring or warming. Thus when 0.34 g. of sodium in 25 cc. of absolute methyl alcohol was added to 4 g. of salt in 10 cc., crystals m. p. 201–203° and weight 3.1 g. were obtained. After extraction with cold water and recrystallization from methyl alcohol, these were dried in a high vacuum at 20°.

Anal. Calcd. for $C_{12}H_{15}O_4N$: C, 60.75; H, 6.36; N, 5.91. Found: C, 60.51; H, 6.61; N, 6.18.

This "ester-salt" is only slightly soluble in absolute methyl alcohol (1 g. in 180 cc. boiling and in 250 cc. at 20°) and water (1 g. in 70 cc. boiling and in 200 cc. at 20°) but dissolves freely in aqueous alkali or acid. When warmed with dilute hydrochloric acid it passed quantitatively into the free imino acid.[5]

The free mono-ethyl ester, VIII, $^+NH_2(CH_2COOC_2H_5)CH(CH_2C_6H_5)COO^-$, m. p. 206–208° (dec.), was obtained when the corresponding dry salt VI was treated with boiling water. A clear colorless solution was first formed, then a gelatinous precipitate which dissolved on heating and finally a white crystalline compound. The latter was pure and the change quantitative in cases where the heating was prolonged for an hour. After recrystallization from boiling water, it was dried in a high vacuum at 20°.

Anal. Calcd. for $C_{13}H_{17}O_4N$: C, 62.14; H, 6.82; N, 5.58. Found: C, 62.30; H, 6.93; N, 5.75.

The "ester-salt" is even less soluble than the corresponding methyl derivative in alcohol (1 g. in 650 cc. boiling) and water but dissolves freely in aqueous alkali and acid. Warmed with dilute hydrochloric acid it passed quantitatively into the free imino acid.[5]

The monamide, IX, $^+NH_2(CH_2CONH_2)CH(CH_2C_6H_5)COO^-$, m. p. 196–197° (dec.), was obtained by passing dry ammonia into an absolute alcohol suspension of either VII or VIII at 20° and concentrating the resulting clear solution. The product was mixed with considerable quantities of the original ester but could be separated by extraction with small quantities of cold water made faintly alkaline with ammonia. Recrystallized from the same solvent, it separated in long, white, silk-like needles which completely filled the space occupied by the solution.

Anal. Calcd. for $C_{11}H_{14}O_3N_2$: C, 59.44; H, 6.35; N, 12.61. Found: C, 59.28; H, 6.66; N, 12.71.

The amide is only slightly soluble in alcohol (1 g. in 200 cc. boiling and in 400 cc. at 20°), but is very soluble in cold water. For example 2 g. in 20 cc., concentrated to 10 cc. under air blast, gives a precipitate of only 1 g., partial hydrolysis being avoided only by the presence of a trace of ammonia. Warmed with dilute hydrochloric acid, the amide passed quantitatively into the imino acid.[5]

Hydantoin-N-1-benzylacetic acid, III, $HOOC(CH_2C_6H_5)CHNCONHCOCH_2$, m. p. 157–158°, was obtained from four compounds (the hydrochlorides V and VI and the esters, VII and VIII) by treating an aqueous alcohol solution or suspension of each with aqueous potassium cyanate slightly in excess of the amount equivalent to the dissociable hydrogen present.

In previewing the course of these reactions it was assumed that if, for example, the compound VII were used as the starting point, primary ionic exchanges (a) would result in the formation of the cyanate, $HOCN \cdot NH(CH_2COOCH_3)CH(CH_2C_6H_5)COOK$. The latter might then be expected to rearrange (b) into the acyclic ureide, $NH_2CON(CH_2COOCH_3)CH(CH_2C_6H_5)COOK$, X; after which ring closure (c) accompanied by the elimination of methyl alcohol and the formation of the hydantoin salt, $KOOC(CH_2C_6H_5)CHNCONHCOCH_2$, XI, might or might not occur. It appeared probable, moreover, that the progress made in each of these transformations could be ascertained by stopping the reaction at the end of different time intervals as a result of adding hydrochloric acid in amounts exactly equivalent to the potassium in the cyanate that had been used in the experiment. Under these conditions, for example, the compound VII would be completely regenerated if no change other than that indicated by (a) had taken place.[24] If, however, even partial rearrangement (b) had occurred, the liberation of the corresponding hydantoic acid almost certainly would be followed by ring closure accompanied by the elimination of water. In this case the product, methyl C-5-benzylhydantoin-N-1-acetate, could also be readily separated and identified.[11] Finally if the transformation indicated by (c) had taken place, a new hydantoin acid, III, isomeric with II, would be formed. Complications arising from alkaline hydrolysis having taken place during the time allowed for the transformations (a), (b) and (c) also were considered. In that event dipotassium derivatives of both the cyanate, and the corresponding ureide X would be formed, *i. e.* $HOCN \cdot NH(CH_2COOK)CH(CH_2C_6H_5)COOK$, and NH_2-

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[22] The filtrate from these crystals gave a gum which was exactly analogous to that described under footnote 16.

[23] The ease with which the mineral acid may be lost has been noted in the case of the salt of the imino acid itself.[5] For other examples compare Stadnikoff, *Ber.*, **41**, 4365 (1908), and **44**, 41 (1911); also Hahn and White, THIS JOURNAL, **54**, 2054 (1932).

[24] This was found actually to be the case when the reaction was stopped at the end of fifteen minutes.

$CON(CH_2COOK)CH(CH_2C_6H_5)COOK$ (I).[1] Introduction of mineral acid would then result in the precipitation of two additional compounds, namely, the free imino acid and the hydantoin-acid II.

In practice the final product was a mixture of all five compounds. For example 4.0 g. of the salt V dissolved in 90 cc. of 80% methyl alcohol was treated with 1.37 g. of solid potassium cyanate and then warmed gently in order to dissolve the resulting precipitate (VII). After cooling to 0° the clear solution was stirred mechanically for one hour, left at room temperature for forty-five hours, concentrated to 20 cc. under air blast and finally treated with 15.7 cc. of 1.018 *N* hydrochloric acid. Extraction with chloroform and then with alcohol-free ether yielded 0.42 and 2.0 g., respectively, of the hydantoin acids II and III and 0.36 g. of the methyl ester of the former, leaving a residue of 0.13 g. of the free imino acid and 0.30 g. of its mono methyl ester. Table I shows the relative percentages of hydantoin derivatives obtained under other conditions.[25]

TABLE I

% Aq. CH_3OH	Reaction period preceding addition of HCl, hr.	% of various products resulting from ring closures III	II	Ester of II
80	1.5	33	Trace only	13.0
80	24	72	Trace only	12.0
65	1.5	40	3.4	11.1
50	1.5	26	26	6.0

In later experiments 80% alcohol was used and excess hydrochloric acid added at the end of twenty-four to forty-eight hours, when the mixture was heated to ensure the hydrolysis of any esters before extracting the acids II and III with chloroform. After evaporation of the chloroform, the mixture was separated by fractional recrystallization from boiling water when III, m. p. 157–158°, was obtained in yields of 70 to 75%.

Anal. Calcd. for $C_{12}H_{12}O_4N_2$: C, 58.06; H, 4.87; N, 11.29. Found: C, 58.02; H, 5.08; N, 11.36.

The hydantoin acid III is not only more soluble than its isomer in water (1 g. in 3 cc. boiling and in 70 cc. at 20°) but when recrystallized from dilute solutions, separates in characteristic rosettes of 30 or more thin, flat hexagonal prisms 2 × 5 mm. at the base but tapering to a sharp point, with a length of 10 to 15 mm.,[26] that can be separated mechanically. Both acids separate as oils from concentrated aqueous solutions, and are very soluble in chloroform but only slightly soluble in ether.

Sodium hydantoin-N-1-benzylacetate was obtained in two different modifications, (a) anhydrous, which began to decompose at 188° and was completely carbonized at 300°, and (b) an alcoholate, which first melted between 60° and 70° with loss of alcohol and then solidified again at 91°. When heated higher this white solid began to decompose at 188° and was completely carbonized at 300°. In both cases the hydantoin-acid III, dissolved in alcohol (3.0 g. in 30 cc.), was treated with aqueous sodium hydroxide (0.4 g. in 5 cc.) and in both cases the product separated in fine white crystals.

Anal. (a) Calcd. for $C_{12}H_{11}O_4N_2Na$: Na, 8.51. Found: Na, 8.71. (b) Calcd. for $C_{12}H_{11}O_4N_2Na \cdot C_2H_5OH$: Na, 7.27; C_2H_5OH, 14.50. Found: Na, 7.39; C_2H_5OH, 13.85.

Both modifications are very soluble in water, only slightly soluble in boiling ethyl alcohol (1.0 g. in 250 cc.) and insoluble in ether. That neither is identical with sodium C-5-benzylhydantoin-N-1-acetate[26] was demonstrated by mixed melting points. Aqueous solutions treated with hydrochloric acid passed quantitatively into the corresponding hydantoin-acid III.

Methyl hydantoin-N-1-benzylacetate, m. p. 105–106.5°, was obtained in 85% yields by passing dry hydrogen chloride into a solution of III in absolute methyl alcohol. The product was separated from traces of III in the usual manner and then recrystallized from boiling 50% alcohol, from which it separated in small, colorless, transparent cubes.

Anal. Calcd. for $C_{13}H_{14}O_4N_2$: C, 59.51; H, 5.30. Found: C, 59.61; H, 5.38.

The ester is extremely soluble in cold methyl alcohol and slightly soluble in boiling water. That it is isomeric and not identical with methyl C-5-benzylhydantoin-N-1-acetate[11] was demonstrated by means of a mixed melting point determination.

Summary

Another example of ring closure accompanied by the elimination of alcohol and the formation of an hydantoin is described, together with the preparation of several new derivatives of β-phenylalanine-N-acetic acid.

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(25) The concentration of V was the same in all experiments, but the heat required for the solution of the ester VII was never satisfactorily controlled and this undoubtedly led to variations in percentage yields not otherwise explained. It may be added that while no appreciable differences were observed when V and VII were used as starting points, the substitution of VI and VIII appeared to result in a definite increase in the speed with which the reaction mixture approached a condition of equilibrium. However, the maximum yields of III from all four compounds were approximately 70% of the theoretical.

(26) Compare Hahn and Endicott, *loc. cit.*, p. 1044.