[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF MOUNT HOLYOKE COLLEGE]

A Further Study of the Cyclization of Ureido Derivatives of Unsymmetrical Iminodibasic Acids Together with the Synthesis of Certain Hydantoins and Other Related Compounds[1]

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Observations have been reported separately to the effect that neither the acyclic ureidic derivative of phenylalanine-N-acetic acid,[2] $NH_2CON(CH_2COOH)CH(CH_2C_6H_5)COOH$, nor the corresponding phenylureide of tyrosine-N-acetic acid,[3] $C_6H_5NHCON(CH_2COOH)CH(CH_2C_6H_4OH)COOH$, has ever been obtained in pure condition. Indeed both appear to be so unstable that when formed by the hydrolysis of their esters or salts, they suffer ring closure almost instantly with the elimination of water and the formation of the corresponding hydantoin derivatives. Attention has not yet been called, however, to the fact that the dimethyl esters of such compounds also show a tendency to cyclization, in this case with the elimination of one molecule of alcohol and the formation of an acetic ester derivative of the corresponding hydantoin.[4] Even more significant is the observation that under all conditions and in the case of all of these diesters and acids only one of the two carboxyl groups enters into a reaction with the ureidic hydrogen atom, although theoretically unsymmetrical dibasic acids of this kind might be expected to form a mixture of two isomeric hydantoins, *i. e.*

(1*a*) $HOOCCH_2\overline{NCONHCOCHCH_2C_6H_5}$ and

(2*a*) $HOOC(CH_2C_6H_5)CH\overline{NCONHCOCH_2}$, or

(1*b*) $HOOCCH_2\overline{NCON(OC_6H_5)COCHCH_2C_6H_4OH}$ and

(2*b*) $HOOC(CH_2C_6H_4OH)CH\overline{NCON(C_6H_5)COCH_2}$

Actually hydantoins of the second type have never been isolated except under conditions which precluded the participation of the substituted acetic acid group in the condensation.[5]

The present investigation was undertaken in order to determine whether a phenylureide of phenylalanine-N-acetic acid, $C_6H_5NHCON(CH_2COOH)CH(CH_2C_6H_5)COOH$, would behave in the same way as the corresponding derivative of tyrosine-N-acetic acid and thus furnish additional evidence in support of the assumption that, in general, substituted acetic acid residues tend to dissociate their hydroxyl groups much more readily than unsubstituted residues. Accordingly a dimethyl ester of the above ureide was prepared by treating the free dimethyl ester of phenylalanine-N-acetic acid, dissolved in absolute ether, with phenyl isocyanate

$$\begin{matrix} & CH_2COOCH_3 \\ NH & \\ & CH(CH_2C_6H_5)COOCH_3 \end{matrix} + C_6H_5NCO \longrightarrow C_6H_5NHCON\begin{matrix} CH_2COOCH_3 \\ CH(CH_2C_6H_5)COOCH_3 \end{matrix}$$

Under these conditions the product separated almost instantly in exceptionally pure condition and in quantitative amounts. Its conversion into methyl N-3-phenyl-C-5-benzylhydantoin-N-1-acetate was effected with equal ease since solution in absolute methyl alcohol containing one equivalent of sodium methoxide[6] was followed within five minutes by precipitation of the calculated quantity of the pure ester. On the other hand, the corresponding hydantoin acid

(1*c*) $HOOCCH_2\overline{NCON(C_6H_5)COCHCH_2C_6H_5}$,

was obtained by the action of aqueous hydrochloric acid upon the acyclic ester. In both cases the condensations were exactly analogous to those previously reported.

The configuration of the hydantoin (1*c*) was subsequently established by means of a separate synthesis which involved the following series of transformations

(1) $NH_2CH_2COOH + C_6H_5NCS \longrightarrow \overline{NHCSN(C_6H_5)COCH_2}$ [7]

(2) $\overline{NHCSN(C_6H_5)COCH_2} + C_6H_5CHO \longrightarrow \overline{NHCSN(C_6H_5)COC{=}CHC_6H_5}$ [8]

(3) The product, N-3-phenyl-2-thio-5-benzalhy-

(1) Grateful acknowledgment is due Dr. Dorothy A. Hahn for suggesting and coöperating in this research.

(2) Hahn and Endicott, THIS JOURNAL, **60**, 1040 (1938).

(3) Ware, *ibid.*, **60**, 2653 (1938).

(4) Hahn, McLean and Endicott, *ibid.*, **62**, 1087 (1940); *cf.* Ware, ref. 3, p. 2655.

(5) Hahn, McLean and Endicott, ref. 4, pp. 1087, 1090, 1091.

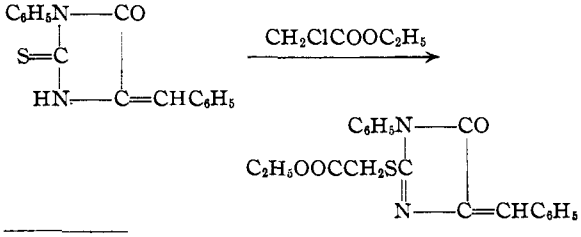
(6) Compare Hahn, McLean and Endicott, ref. 4, p. 1088, footnote 8.

(7) Brautlecht, *J. Biol. Chem.*, **10**, 142 (1911); cf. Aschan, *Ber.*, **16**, 1544 (1883) and **17**, 424 (1884); also Marckwald, Neumark and Stelzner, *ibid.*, **24**, 3276 (1891).

(8) Wheeler and Brautlecht, *Am. Chem. J.*, **45**, 448 (1911).

dantoin, which will be referred to again in another connection, was then converted into the corresponding oxy-compound, $\overline{NHCON(C_6H_5)COC}=CHC_6H_5$,[9] by first preparing the ethyl mercapto derivative and then hydrolyzing this in the presence of hydrochloric acid. (4) and (5) The preparation of ethyl N-3-phenylbenzalhydantoin-N-1-acetate[10] was carried out in the usual way[11] and the product then reduced and hydrolyzed simultaneously under the action of hydrogen iodide and red phosphorus.[12] The product finally obtained as a result of the above series of transformations was N-3-phenyl-5-benzylhydantoin-N-1-acetic acid. That it was identical with the compound (1*c*) previously obtained from the corresponding acyclic ureide, was established by a mixed melting point as well as by a detailed comparison of the properties of the two substances.

Supplementary work undertaken during the course of this investigation will now be outlined briefly since, although minor in character, it adds a few facts to what has been previously reported regarding the behavior of three of the substances which have been mentioned. Of these, N-3-phenyl-2-thiobenzalhydantoin[8] and ethyl N-3-phenylbenzalhydantoin-N-1-acetate[10] will be considered first.[13] The thiohydantoin has been observed, for example, to condense readily not only with ethyl chloride to form a mercapto derivative in the manner described by Wheeler and Brautlecht, but also to react almost instantly with α-halogen derivatives of esters of the fatty acids. In the case of ethyl chloroacetate, the reaction takes place as follows



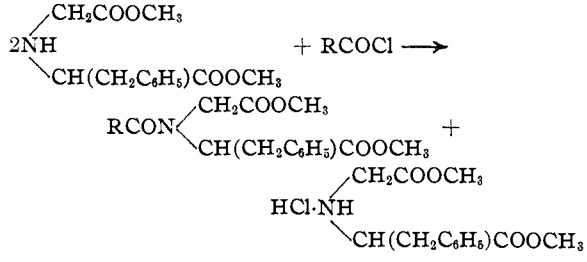
and in the presence of ethyl phenylbromoacetate or ethyl bromopropionate analogous compounds may be obtained. That all of these compounds are true mercapto derivatives was demonstrated by the fact that each, like 2-ethylmercapto-3-phenyl-5-benzalhydantoin, was converted into N-3-phenyl-2-oxybenzalhydantoin when hydrolyzed in the presence of hydrochloric acid.

A study of ethyl N-3-phenylbenzalhydantoin-N-1-acetate revealed that it reacted in a manner closely analogous to ethyl N-3-methylbenzalhydantoin-N-1-acetate when treated with bromine under certain specific conditions,[14] and that two isomeric unsaturated monobromo derivatives were formed. These appear to represent geometric modifications of a compound possessing the following structure

$$C_2H_5OOCCH_2\overline{NCON(C_6H_5)COC}=CBrC_6H_5$$

and may, therefore, be assumed to have resulted from the elimination of hydrogen bromide from a primary dibromo addition product.[15]

A third and somewhat more extended investigation was concerned with an effort to prepare N-acyl derivatives of phenylalanine-N-acetic acid, but in this case only a few positive results were obtained. The free dimethyl ester was first used as a starting point and the experiments carried out by applying Fischer's method of procedure[16]



Since the reaction takes place in an absolute ether solution, its progress can be followed by the separation of the insoluble hydrochloride. However, from among a number of different reagents employed in these experiments positive reactions were observed only in the case of three, namely, acetyl chloride, benzoyl chloride and 3,5-dinitrobenzoyl chloride. Even then only one primary product, *i. e.*

$3,5\text{-}(NO_2)_2C_6H_3CON(CH_2COOCH_3)CH(CH_2C_6H_5)COOCH_3$

could be obtained in pure crystalline condition

(9) Wheeler and Brautlecht, ref. 8, p. 451. The product, N-3-phenylbenzalhydantoin, was also prepared by condensing N-3-phenylhydantoin with benzaldehyde according to the method of Wheeler and Hoffman [*Am. Chem. J.*, **45**, 368 (1911)], a reaction which though mentioned as practical by Johnson and Brautlecht [THIS JOURNAL, **33**, 1531 (1911)], was never described in detail. The compound prepared in this way was found to be identical with that prepared by the method of Wheeler and Brautlecht.

(10) Halogen derivatives of this compound will be considered later.

(11) and (12) Compare Litzinger, THIS JOURNAL, **56**, 673, 675 (1934).

(13) Investigations concerning derivatives of these two substances were carried out, respectively, by Shirley M. Vincent and Marian L. Blanchard in connection with work that led to the B.A. degree with Honors in June, 1941.

(14) McLean and Seeger, THIS JOURNAL, **62**, 1416 (1940).

(15) Hahn, McLean and Murphy, *ibid.*, **60**, 1927 (1938); also *cf.* Litzinger, refs. 11, 12, p. 677.

(16) Fischer and Otto, *Ber.*, **36**, 2112 (1903); *cf.* Kossel, *ibid.*, **24**, 4153 (1891).

and in quantitative yields, all other products separating from their ether solution in the form of oils. Of these the acetyl derivative dissociated readily into its components since when its ether solution was treated with dry hydrogen chloride, the hydrochloride of the imino ester was precipitated quantitatively. The benzoyl derivative, on the other hand, was sufficiently stable to admit of transformation into the corresponding disodium salt. The latter formed a well defined crystalline compound which was subsequently identified by comparison with a product resulting from the application of the Schotten–Baumann reaction to phenylalanine-N-acetic acid itself. It may be added that although the latter method of acylation was applied in the case of other reagents, the only compound which was obtained in a condition sufficiently pure for analysis was *m*-nitrobenzoylphenylalanine-N-acetic acid, *m*-$NO_2C_6H_4$-$CON(CH_2COOH)CH(CH_2C_6H_5)COOH \cdot 2H_2O$.

Experimental

The phenylalanine-N-acetic acid[17] and the hydrochloride of the corresponding dimethyl ester[18] were prepared by methods previously reported. However, the yields of the latter were increased from 70% to nearly 100% by surrounding the reaction flask with an ice-bath during saturation with dry hydrogen chloride and then allowing the closed flask to remain for four days at room temperature. The product, when recrystallized from boiling acetone, melted at 144–144.5° with an evolution of gas.

Dimethyl phenylalanine-N-acetate, $NH(CH_2COOCH_3)$-$CH(CH_2C_6H_5)COOCH_3$, was prepared by treatment of the corresponding hydrochloride with an exact equivalent of aqueous sodium carbonate and extraction with ether. It boiled sharply at 182° (10 mm.).

Anal. Calcd. for $C_{13}H_{17}O_4N$: C, 62.13; H, 6.82; N, 5.58. Found: C, 62.11; H, 6.78; N, 5.73.

Dimethyl Ureidophenylalanine-N-acetate, NH_2CON-$(CH_2COOCH_3)CH(CH_2C_6H_5)COOCH_3$, was prepared by adding 0.88 g. of powdered potassium cyanate to a solution of 2 g. of the above ester hydrochloride in 5 cc. of water. The product, an oil which crystallized on stirring, consisted of a mixture of the ureide and methyl 5-benzylhydantoin-N-1-acetate,[19] the latter having formed by ring closure. Although it was impossible to effect complete separation of these two substances, a crystalline compound (m. p. 125–126°) was obtained from absolute methyl alcohol.[20]

Anal. Calcd. for $C_{14}H_{18}O_5N_2$: C, 57.12; H, 6.16; N, 9.52. Found: C, 58.80; H, 5.77; N, 9.52.

Dimethyl Phenylureidophenylalanine-N-acetate, $C_6H_5NHCON(CH_2COOCH_3)CH(CH_2C_6H_5)COOCH_3$, was obtained by adding 1.3 cc. of phenyl isocyanate, dropwise under cooling and stirring, to a solution of 2 g. of dimethyl phenylalanine-N-acetate in 200 cc. of absolute ether. The heavy white crystalline precipitate which began to form almost immediately and was complete at the end of two hours, weighed 1.7 g. and melted to a clear liquid at 124.5–125°. Additional amounts recovered from the filtrate made the yield quantitative.

Anal. Calcd. for $C_{20}H_{22}O_5N_2$: C, 64.85; H, 5.99; N, 7.56. Found: C, 64.42; H, 5.78; N, 7.83.

The ureidic ester is very soluble in methyl alcohol, acetone and chloroform; moderately soluble in ether, carbon tetrachloride and boiling water and almost insoluble in cold water. The corresponding acyclic dibasic acid was never obtained since hydrolysis of the ester in the presence of aqueous hydrochloric acid is accompanied simultaneously by ring closure.

$CH_3OOCCH_2\overline{NCON(C_6H_5)COCHCH_2C_6H_5}$, **Methyl N-3-phenyl-5-benzylhydantoin-N-1-acetate,** m. p. 97–97.5°, was obtained by dissolving 3 g. of dimethyl phenylureidophenylalanine-N-acetate in absolute alcohol which contained one equivalent of sodium methoxide (0.19 g. of sodium in 12 cc.).[21] The product precipitated immediately as fine white needles (2.21 g.) and was recrystallized from 50% methyl alcohol (1 g. in 4.4 cc. boiling). Since additional quantities could not be separated from the filtrate, the latter was evaporated to dryness and the residue dissolved in aqueous hydrochloric acid, when 0.45 g. of the corresponding hydantoin acid, m. p. 159–160°, separated, thus bringing the total yield to 98% of the theoretical.

Anal. Calcd. for $C_{19}H_{18}O_4N_2$: C, 67.44; H, 5.36; N, 8.28. Found: C, 67.50; H, 5.22; N, 8.55.

This ester is very soluble in methyl alcohol (1 g. in 0.3 cc. boiling and in 1.2 cc. at 20°) and in acetone (1 g. in 0.5 cc. boiling and in 3.5 cc. at 20°). It is extremely stable in the presence of 10% hydrochloric acid (less than 40% being hydrolyzed as a result of heating an aqueous alcohol solution for eight hours) while in the presence of alkali its hydrolysis was accompanied by the formation of decomposition products.[22]

$HOOCCH_2\overline{NCON(C_6H_5)COCHCH_2C_6H_5} \cdot 2H_2O$, **N-3-Phenyl-5-benzylhydantoin-N-1-acetic** acid (1*c*), was obtained in a number of different ways. As previously stated, it resulted from the hydrolysis of dimethyl phenylureidophenylalanine-N-acetate, since the corresponding acyclic acid, $C_6H_5NHCON(CH_2COOH)CH(CH_2C_6H_5)$-$COOH$, is unstable and suffers ring closure the moment it is liberated. The same hydantoin acid was also synthesized from phenylalanine-N-acetic acid by dissolving the latter (5 g.) in aqueous sodium bicarbonate and treating the ice-cold solution with phenyl isocyanate (4 g.) added over a period of four hours under constant stirring, after which the mixture was allowed to stand overnight at room temperature. Following the removal of a small amount of *sym*-diphenyl urea, the clear liquid was diluted to a volume of 500 cc. and treated with 20 cc. of concentrated hydrochloric acid when a heavy oil separated. The latter was transformed into fine white crystals (6.75 g.) by heating

(17) Hahn and Endicott, ref. 2, p. 1042.

(18) Hahn, McLean and Endicott, ref. 4, p. 1089.

(19) Hahn and Endicott, ref. 2, p. 1044.

(20) This compound on hydrolysis suffered ring closure and passed quantitatively into 5-benzylhydantoin-N-1-acetic acid. *Cf.* Hahn and Endicott, ref. 2, p. 1043.

(21) *Cf.* Bailey and Snyder, THIS JOURNAL, **37**, 391 (1915).

(22) That hydrolysis was extensive is shown by the fact that a sodium salt of phenylalanine-N-acetic acid was isolated.

the reaction mixture, and additional quantities obtained from the filtrate made the yield quantitative. The acid, crystallized from boiling water, separated in large transparent prisms which decrepitate at 95° with an evolution of a gas and on exposure to the air, slowly decompose and become opaque. Heated at 110° they lost two molecules of water rapidly, passing into the anhydrous form which melts sharply at 159.5–160°

Anal. Calcd. for $C_{18}H_{16}O_4N_2 \cdot 2H_2O$: C, 59.99; H, 5.59; N, 7.78; H_2O, 9.91. Found: C, 59.86; H, 5.69; N, 8.20; H_2O, 9.96. Calcd. for $C_{18}H_{16}O_4N_2$: C, 66.68; H, 4.97; N, 8.64. Found: C, 66.87; H, 4.99; N, 8.80.

Since the acid is only slightly soluble in water (1 g. in 400 cc. of boiling and in 2500 cc. at 20°) while very soluble in alcohol (1 g. in 0.4 cc. of boiling and in 2 cc. at 20°), it was conveniently recrystallized from 50% alcohol. It is also very soluble in boiling methyl alcohol (1 g. in 1.8 cc.) and in cold acetone (1 g. in 1.5 cc.), glacial acetic acid and chloroform. It is readily transformed into the corresponding methyl ester when dissolved in methyl alcohol and treated with dry hydrogen chloride.

The configuration of both N-3-phenyl-5-benzylhydantoin-N-1-acetic acid and its methyl ester was finally established by means of a separate synthesis as follows.

$\overline{NHCON(C_6H_5)COC}=CHC_6H_5$, **N-3-Phenyl-5-benzalhydantoin,** m. p. 252–252.5°, was prepared by condensing N-3-phenylhydantoin[23] with benzaldehyde according to the method of Wheeler and Hoffman[24] which consisted in refluxing a mixture of 75 g. of phenylhydantoin, 52 g. of freshly distilled benzaldehyde, 78 g. of fused sodium acetate and 350 cc. of glacial acetic acid for eleven hours. The reaction mixture was then diluted with an equal volume of water, and the product, N-3-phenyl-5-benzalhydantoin[25] (91.78 g.), was freed from traces of the reactants by washing first with boiling water and then with cold alcohol.

The compound is almost insoluble in boiling water; slightly soluble in boiling alcohol (1 g. in 400 cc.) and very soluble in glacial acetic acid (1 g. in 33 cc. boiling and in 224 cc. at 20°) from which it was recrystallized.

Anal. Calcd. for $C_{16}H_{12}O_2N_2$: C, 72.71; H, 4.57; N, 10.60. Found: C, 72.85; H, 4.40; N, 10.78.

$C_2H_5OOCCH_2\overline{NCON(C_6H_5)COC}=CHC_6H_5$, **Ethyl N-3-phenyl-5-benzalhydantoin-N-1-acetate,** m. p. 88.5–89°, was obtained by treating a solution of N-3-phenyl-5-benzalhydantoin (30 g.) in 225 cc. of absolute alcohol containing 3.3 g. of sodium, with freshly distilled ethyl chloroacetate (19.5 g.) and refluxing for eighteen hours after which the precipitate (largely sodium chloride) was filtered and washed with boiling alcohol in which the ester is very soluble. Dry hydrogen chloride gas was then passed into the alkaline solution in order to precipitate phenylbenzalhydantoin (in all 6.5 g. was recovered) from any N-1 sodium salt that remained in solution. The hot filtrate from this second precipitate (volume 850 cc.) when concentrated deposited the product in theoretical amounts, calculated on the phenylbenzalhydantoin that had reacted. The ester crystallized from alcohol as white transparent plates.

Anal. Calcd. for $C_{20}H_{18}O_4N_2$: C, 68.56; H, 5.17; N, 8.00. Found: C, 68.69; H, 5.06; N, 8.22.

The product is readily soluble in alcohol (1 g. in 3 cc. boiling and in 100 cc. at 20°), cold acetone, ether and chloroform. All attempts to prepare a geometric isomer of this ester were fruitless although two modifications are theoretically possible and have been isolated in other cases.[26]

The transformation of this unsaturated ester into the corresponding saturated acid, which served to establish the configuration of the latter, was accomplished in the following way. The ester (20 g.), mixed with hydrogen iodide (54 cc., sp. g. 1.7) and red phosphorus (3.5 g.), was heated over a metal bath kept at a temperature of 140–145° until no further distillate was given off after which the excess hydrogen iodide was removed under reduced pressure. The residue was then extracted with boiling water and finally the product was extracted from the red phosphorus with boiling alcohol. The filtrate was concentrated to 100 cc. and treated with an equal volume of boiling water. On cooling it deposited 16.8 g. of the crystalline hydrate additional quantities of which were recovered from the filtrate, indicating a quantitative reaction. This acid was not only identical in all respects with that obtained from the interaction of phenylalanine-N-acetic acid and phenyl isocyanate, but it formed a methyl ester which was the same as that obtained from dimethyl phenylureidophenylalanine-N-acetate as a result of ring closure.

As stated in the introduction, two of the unsaturated hydantoins which were prepared during the course of the above investigation were made the subjects of special study. Of these the first, N-3-phenyl-2-thiobenzalhydantoin,[8] was transformed into three new mercapto derivatives and the second, ethyl N-3-phenyl-5-benzalhydantoin-N-1-acetate,[10] into two isomeric monobromo substitution products. A description of the experimental work follows.

N-3-Phenyl-2-thio-5-benzalhydantoin, prepared according to the method of Wheeler and Brautlecht,[8] was first transformed into the corresponding 2-ethylmercapto derivative[27] as a check on subsequent experiments. It was then treated with ethyl chloroacetate, ethyl phenylbromoacetate and ethyl α-bromopropionate, respectively, under exactly analogous conditions, *i. e.*, 10 g. of the hydantoin, dissolved in 75 cc. of absolute alcohol containing 1.1 equivalents of sodium, reacting with a slight excess of the reagent. In each case the transformation was either instantaneous or complete after the mixture had been heated for thirty minutes, and on cooling the product separated in almost pure condition in the form of pale yellow needles or plates. Yields varied from 86 to 96% of the theoretical value depending somewhat upon the solubility of the compound, which was recrystallized from alcohol. The melting points, solubilities in alcohol and analyses of the individual products are listed below.

(23) Prepared according to the method developed by Paal, *Ber.*, **27**, 975 (1894), and Mouneyrat, *ibid.*, **33**, 2393 (1900).

(24) Wheeler and Hoffman, *Am. Chem. J.*, **45**, 368 (1911). This reaction was mentioned as practical by Johnson and Brautlecht (ref. 9) but never described in detail.

(25) This compound, when prepared from N-3-phenyl-2-thio-5-benzalhydantoin, was reported by Wheeler and Brautlecht (ref. 8, p. 451) to melt between 242° and 243°. This melting point can be raised ten degrees by repeated recrystallizations.

(26) Compare Litzinger, ref. 11, p. 673; Hahn and Gilman, THIS JOURNAL, **47**, 2953–61 (1925).

(27) Wheeler and Brautlecht, ref. 8, p. 450.

$N{=}CS(CH_2COOC_2H_5)N(C_6H_5)COC{=}CHC_6H_5$, **Ethyl N-3-phenyl-5-benzalhydantoin-2-mercaptoacetate,** m. p. 142–144°; 1 g. in 21 cc. boiling and in 325 cc. at 20°.

Anal. Calcd. for $C_{20}H_{18}O_3N_2S$: C, 66.55; H, 4.95; N, 7.65; S, 8.75. Found: C, 66.51; H, 5.31; N, 7.72; S, 8.68.

$N{=}CS[CH(C_6H_5)COOC_2H_5]N(C_6H_5)COC{=}CHC_6H_5$, **Ethyl N-3-phenyl-5-benzalhydantoin-2-mercaptophenylacetate,** m. p. 156–156.5°; 1 g. in 40 cc. boiling and in 400 cc. at 20°.

Anal. Calcd. for $C_{26}H_{22}O_3N_2S$: C, 70.57; H, 5.01; N, 6.33; S, 7.25. Found: C, 70.14; H, 5.06; N, 6.55; S, 7.24.

$N{=}CS[CH(CH_3)COOC_2H_5]N(C_6H_5)COC{=}CHC_6H_5$, **Ethyl N-3-phenyl-5-benzalhydantoin-2-mercaptopropionate,** m. p. 111–112°; 1 g. in 7 cc. of boiling and in 150 cc. at 20°.

Anal. Calcd. for $C_{21}H_{20}O_3N_2S$: C, 66.30; H, 5.30; N, 7.36; S, 8.43. Found: C, 65.76; H, 5.07; N, 7.41; S, 8.08.

All three compounds when dissolved in alcohol and boiled for fifteen minutes with concentrated hydrochloric acid passed quantitatively into N-3-phenyl-5-benzalhydantoin,[9] their behavior being analogous to that of 2-ethylmercapto-N-3-phenyl-5-benzalhydantoin.

$C_2H_5OOCCH_2NCON(C_6H_5)COC{=}CBrC_6H_5$, **Ethyl N-3-phenyl-5-α-bromobenzalhydantoin-N-1-acetate,** exists in two isomeric modifications: *a*, m. p. 124–125°, and *b*, m. p. 98–100°, which were formed simultaneously when ethyl N-3-phenyl-5-benzalhydantoin-N-1-acetate,[10] dissolved in glacial acetic acid, was treated with a molecular equivalent of bromine.[28] During the process of eliminating hydrogen bromide from the reaction mixture the acetic acid was gradually displaced by carbon tetrachloride. On evaporation of the solvent, the product separated as a heavy oil which was partially resolved into its components by fractional crystallization from 60% alcohol, the ester *a* being relatively less soluble than *b*. Purification was complicated by the fact that both compounds are extremely soluble in all solvents and tend to form oily mixtures. Moreover, the substance[10] from which they were obtained is almost equally soluble.

Anal. Calcd. for $C_{20}H_{17}N_2O_4Br$: C, 55.44; H, 3.99; N, 6.53; Br, 18.61. Found: *a*, m. p. 124–125°, C, 56.30; H, 3.60; N, 6.84; Br, 18.42. Found: *b*, m. p. 98–100°, C, 55.98; H, 3.92; N, 6.98; Br, 18.89.

As stated in the introduction, dimethyl phenylalanine-N-acetate was treated successively with a number of different acyl chlorides. The procedure, which was the same in all cases, consisted in treating a solution of 2 g. of the free ester in 200 cc. of ether with one-half of a molecular equivalent of the acid chloride. In cases where a reaction took place, separation of the hydrochloride of the ester began immediately and was complete at the end of two hours; in cases where no precipitate had formed at the end of five hours, the original ester was recovered in quantitative amounts in the form of its hydrochloride by passing dry hydrogen chloride into the solution.

(28) *Cf.* McLean and Seeger, ref. 14, p. 1418.

$(NO_2)_2C_6H_3CON(CH_2COOCH_3)CH(CH_2C_6H_5)COOCH_3$, **Dimethyl 3,5-dinitrobenzoylphenylalanine-N-acetate,** m. p. 102–103°, formed in quantitative yield and crystallized from absolute alcohol in fine white needles growing in clusters.

Anal. Calcd. for $C_{20}H_{19}O_9N_3$: C, 53.91; H, 4.30; N, 9.43. Found: C, 53.57; H, 4.21; N, 9.71.

Attempts to transform this product into either the corresponding acid or salt were unsuccessful.

Dimethyl benzoylphenylalanine-N-acetate, $C_6H_5CON(CH_2COOCH_3)CH(CH_2C_6H_5)COOCH_3$, was obtained in the form of a heavy oil which refused to crystallize. That the product consisted exclusively of an ester of the benzoyl derivative was shown by the fact that an ether solution of the oil gave no precipitate when treated with dry hydrogen chloride. Moreover, when warmed with two equivalents of sodium hydroxide dissolved in aqueous alcohol, the ester passed quantitatively into the corresponding disodium salt. The latter, recrystallized from aqueous alcohol, melted at 288–289° (dec.) and was identified by means of the following synthesis.

Disodium benzoylphenylalanine-N-acetate, $C_6H_5CON(CH_2COONa)CH(CH_2C_6H_5)COONa\cdot 2H_2O$, m. p. 288–289° (dec.), was prepared by treating a solution of 5 g. of phenylalanine-N-acetic acid and two equivalents (3.8 g.) of sodium bicarbonate in 45 cc. of water with three equivalents of benzoyl chloride and six equivalents of sodium bicarbonate, the reagents being added alternately over a period of twelve hours. Concentrated hydrochloric acid was then added in excess, the precipitated gum taken up in ether and the solution extracted with the same solvent. In this way the benzoic acid and the benzoyl derivative of phenylalanine-N-acetic acid were separated from any imino dibasic acid which had failed to react (1.06 g.),[29] the latter remaining in solution as the hydrochloride. The combined ether extractions were then extracted with 10% sodium hydroxide, and the salt solution was concentrated to 10 cc. and treated with an equal volume of boiling absolute alcohol. Upon standing overnight 2.19 g. of thin, white, glistening plates separated and when absolute alcohol was added to successively concentrated filtrates, additional quantities (3.5 g.) of the same substance were obtained.[30] The salt was purified by treating its cold aqueous solution (1 g. in 2 cc.) with an equal volume of absolute alcohol.

Anal. Calcd. for $C_{18}H_{15}O_5NNa_2\cdot 2H_2O$: C, 53.09; H, 4.70; N, 3.44; Na, 11.29. Found: C, 53.01; H, 4.45; N, 3.64; Na, 11.06.

During the process of recrystallization an isomeric salt *b*, which melted sharply at 272–273° (dec.), was isolated. The latter, which appeared to be much more soluble in 50% alcohol than the compound, m. p. 288–289°, also separated as white, glistening plates. The configuration of these salts is uncertain. It may be noted also that neither on heating at 110° loses its water of crystallization, although the presence of two molecules is indicated from the results of analysis.

(29) This was identified following the hydrolysis of the hydrochloride; *cf.* Hahn and Endicott, ref. 2, p. 1041, footnote 4.

(30) In all, the yield corresponded to 86% of the theoretical as calculated upon the number of grams of imino acid which had reacted.

Anal. *b*. Calcd. for $C_{18}H_{16}O_5NNa_2 \cdot 2H_2O$: C, 53.09; H, 4.70; Na, 11.29. Found: C, 53.09; H, 4.41; Na, 11.26.

***m*-Nitrobenzoylphenylalanine-N-acetic acid,** $NO_2C_6H_4CON(CH_2COOH)CH(CH_2C_6H_5)COOH \cdot 2H_2O$, was obtained in two different crystalline modifications, one of which (*a*) melts at 90–92° and decomposes with the evolution of a gas at 105°, while the other (*b*) remains unchanged until 105° when it decrepitates with the evolution of a gas, melting at 130–131° (dec.). Both substances were formed under the conditions described above except that potassium hydroxide was used in place of the sodium bicarbonate and it was found expedient to spread the addition of the *m*-nitrobenzoyl chloride and alkali over a period of thirty-six hours. Moreover, following the addition of hydrochloric acid, a gum was precipitated which crystallized on treatment with ether, yielding 3.81 g. of the product *a* in the form of thin creamy-white, glistening plates. Additional quantities obtained from the filtrate brought the percentage yield to approximately 65% of the theoretical value. The product was recrystallized from water (1 g. soluble in 50 cc. boiling and in 100 cc. at 20°).

The product *b*, isolated in small quantities during the process of recrystallizing *a*, has the same crystalline form but is more soluble in water.

Anal. Calcd. for $C_{18}H_{16}O_7N_2 \cdot 2H_2O$: C, 52.91; H, 4.94; N, 6.88. Found: *a*, C, 52.71; H, 4.79; N, 7.19. Found: *b*, C, 52.20; H, 5.02; N, 7.25.

Summary

Both dimethyl phenylureidophenylalanine-N-acetate and the corresponding acyclic dibasic acid undergo condensation, with the elimination of one molecule of methyl alcohol and one molecule of water, respectively, to form in each case only one of the two isomeric cyclic compounds which might be expected on the basis of purely theoretical considerations. These results agree with previous observations in showing that a marked difference exists between the reactivities of the two acid complexes present in certain unsymmetrical iminodibasic acids. Moreover, the configuration of the product, which has been definitely established in each case, indicates that in all instances so far reported ring closure always takes place in the same general sense.

New derivatives of N-3-phenyl-2-thiobenzalhydantoin and of ethyl N-3-phenylbenzalhydantoin-N-1-acetate are described, together with others obtained by the action of certain acyl chlorides upon phenylalanine-N-acetic acid and its dimethyl ester.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE UNIVERSITY OF RICHMOND]

Local Anesthetics. I. β-Monoalkylaminoethyl Esters of Alkoxybenzoic Acids[1]

BY J. STANTON PIERCE, J. M. SALSBURY AND J. M. FREDERICKSEN

The majority of the synthetic local anesthetics are alkamine esters of the type $XC_6H_4COO(CH_2)_yNR_2$ in which X usually is the primary amino group, *y* is 2 or 3, and R is an alkyl group. Goldberg and Whitmore[2] have demonstrated that the tertiary amino group, above, can be replaced advantageously by a secondary amino group. Other investigators[3] have shown that in the above type formula, X can be an alkoxy group. This investigation takes up the preparation of alkamine esters of the type $ROC_6H_4COOCH_2CH_2NHR'$.

Most of the alkoxybenzoic acids reported in this work have been made by previous investigators.[4] For this investigation the alkoxybenzoic acids not obtainable from Eastman Kodak Co. were made from the methyl or ethyl ester of the phenolic acid, according to the method of Cohen and Dudley,[4a] by the alkylation of the ester with alkyl bromide and hydrolysis of the ester.

The alkoxybenzoyl chlorides were prepared from the alkoxybenzoic acids and phosphorus pentachloride in all but one case, that of *p*-allyloxybenzoic acid, when phosphorus trichloride was used.

Most of the β-monoalkylaminoethanols were prepared by the reaction of an alkyl halide with a large excess of ethanolamine, without a solvent. Goldberg[5] recommends the use of approximately equimolar quantities of alkyl bromide and ethanolamine, in alcohol solution. This procedure was not found to be satisfactory for the formation of β-mono-*n*-butylaminoethanol, β-mono-*n*-propylaminoethanol, β-monoallylaminoethanol, and β-

(1) Acknowledgment is made to Dr. E. Emmet Reid, Research Adviser to the Chemistry Department of the University of Richmond, for his advice during the course of this work.

(2) Goldberg and Whitmore, THIS JOURNAL, **59**, 2280 (1937).

(3) Wildman and Thorp, U. S. Patent 1,193,650 (1916); C. Rohmann and Scheurle, *Arch. Pharm.*, **274**, 110–126 (1936).

(4) (a) J. B. Cohen and H. W. Dudley, *J. Chem. Soc.*, 1732–1751 (1910); (b) A. E. Bradfield and B. Jones, *ibid.*, 2660–2661 (1929); (c) B. Jones, *ibid.*, 1874 (1935); (d) Bennett and Jones, *ibid.*, 420 (1939); (e) Lauer, Sanders, Leekley and Ungnade, THIS JOURNAL, **61**, 3050 (1939).

(5) S. D. Goldberg, U. S. Patent 2,139,818 (1938).