Studies on α -Alkyl- α -amino AcidsPart II. Hydantoins Containing Chlorines on the Side-chain
and their Alkaline Hydrolysis Products

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In the previous paper,¹⁾ the authors mentioned the synthesis of two hydantoins containing chlorines in addition to twelve 5-alkylthiomethyl-5-methylhydantoins which were hydrolyzed to corresponding S-alkyl-2-methyl-DL-cysteines. Hydantoins containing chlorines were confirmed to be 5-monochloromethyl-5-methylhydantoin (I) and 5-dichloromethyl-5-methylhydantoin (II), respectively. In this note, the authors deal with three other chlorine containing hydantoins, 5-chloromethyl-5-ethylhydantoin (III), 5-(1-chloroethyl)-5-methylhydantoin (IV) and 5-trichloromethylhydantoin (V), and further with alkaline hydrolysis of I, II and V. Hydantoins were prepared by the method of Bucherer.²⁾ III

and IV were derived from two isomers of chlorobutanone respectively and V was from chloral hydrate.

Yields of III, IV and V were extremely lower than in the case of other carbonyl compounds.^{1,2)} Reaction conditions should be improved. Hydantoins were hydrolyzed in about 1M Ba(OH)₂ solution.³⁾ The barium ions were removed as barium carbonate and further desalted by passing the solution through columns of anion and cation exchange resins. Ninhydrin positive products were detected by paper chromatography (PC) and thin-layer chromatography (TLC).⁴⁾ Constituents were isolated by column chromatography on cellulose powder. As shown in Fig. 1,

TABLE I. HYDANTOINS CONTAINING CHLORINES

	Substituent groups		Mp (°C)	Starting materials	
	R ₁	R ₂			
I	CH ₃	CH ₂ Cl	141~2	Chlorinated acetones bp 114~120°C
II	CH ₃	CHCl ₂	241~3		
III	CH ₂ Cl	CH ₃ CH ₂	185~6	1-Chloro-2-butanone	
IV	CH ₃	CH ₃ CHCl	231~2	3-Chloro-2-butanone	
V	H	CCl ₃	98~100*	Chloral hydrate	

* dihydrate, see experimental.

1) S. Tahara and Y. Obata, *Agr. Biol. Chem.*, **35**, 53 (1971).2) H. T. Bucherer and V. A. Lieb, *J. prakt. Chem.*, **141**, 5 (1934).3) K. T. Potts, *J. Chem. Soc.*, **1955**, 1632.

4) Filter paper of Toyo Roshi No. 50 was used for PC and thin-layer plate of Avisel SF (Asahi Kasei Co., Ltd.) for TLC.

FIG. 1. Paper Chromatogram of Alkaline Hydrolyzates of I and II.

The chromatogram of desalted hydrolyzates of I, II and authentic samples was developed with a solvent system of n -BuOH : AcOH : H₂O = 4 : 1 : 1 for three times by the ascending technique. Abbreviations: α -AIB, α -aminoisobutyric acid; 2-MS, 2-methylserine.

the hydrolyzate of I consists of main three (Spot 1, Spot 2 and Spot 3) and other three spots or so. R_f values of Spot 1 and Spot 2 are corresponding to that of authentic alanine and 2-methylserine, respectively.

Isolated Spot 2 was crystallized and the result of elementary analysis indicated it to be 2-methylserine (VI). VI was synthesized by Zelinsky and Dengin,⁵¹ and Billman and Parker,⁶¹ and reported to be an hydrolysis product of the antibiotic Amicetin.⁷¹ As the

Spot 3 was very hygroscopic, no further investigation was continued.⁸¹ It was plausibly considered that VI was a direct hydrolysis product of I and that alanine was derived from VI by the reverse-aldol reaction with alkali.

Alanine was obtained in the yield of 90.4% (nearly quantitatively) from the hydrolyzate of II. It seems reasonable to assume that after the $-\text{CHCl}_2$ group was hydrolyzed, the decarbonylation or decarboxylation reaction took place. One might be interested in the reaction mechanisms, but details were not understood. Only one ninhydrin positive spot in the hydrolyzate of V expectedly coincided in position with that of authentic glycine on the chromatograms.

EXPERIMENTAL

All hydantoins, alanine and 2-methylserine are the racemic modifications and melting points were uncorrected.

5-Chloromethyl-5-methylhydantoin (I) and its hydrolysis products. The preparation method of I was essentially as same as that reported in the previous paper.¹¹

I, mp 141~142°C; NMR $\tau_{\text{DSS}}^{\text{D}_2\text{O, NaOD}}$: 8.50 (3H, s, $-\text{C}-\text{CH}_3$), 4.01 (2H, s, $-\text{C}-\text{CH}_2\text{Cl}$), and *Anal.* Found: C, 36.79; H, 4.36; N, 17.09. Calcd. for C₅H₇O₂N₂Cl: C, 36.94; H, 4.34; N, 17.23%. The infrared spectrum is shown in Fig. 2. Thirty grams of I was hydrolysed with aqueous barium hydroxide (250 g of Ba(OH)₂·8H₂O and 600 ml of water) under reflux for 50 hr. After the evolution of ammonia had weakened, CO₂ gas was introduced and barium ions were precipitated as barium carbonate from the solution at 100°C. The filtrate and washings were concentrated under reduced pressure. The concentrated reaction mixture was diluted about three times with methanol and inorganic precipitate was filtered off. The filtrate diluted with water was desalted with ion exchange

5) N. D. Zelinsky and E. F. Dengin, *Ber.*, **55**, 3354 (1922).

6) J. H. Billman and E. E. Parker, *J. Am. Chem. Soc.*, **67**, 1069 (1945).

7) E. H. Flynn, J. W. Hinman, E. L. Caron and D. O. Woolf, Jr., *ibid.*, **75**, 5867 (1953).

8) But after the almost pure Spot 3 dissolved in a solution of 1 M Ba(OH)₂ was maintained in a sealed tube at 130°C for 24 hr, new two spots considered to be alanine and 2-methylserine were detected by PC and TLC. The result may imply the Spot 3 to be intermediate in the course of hydrolysis of I.

FIG. 2. The IR Spectrum of 5-Chloromethyl-5-methylhydantoin (I) (KBr).

resins, dowex 1-X2 followed by dowex 50W-X2. One-sixth of desalted and concentrated hydrolyzate, containing 3.3 g of dried matter was applied to a column of cellulose powder⁹⁾ (3×45 cm) which had been saturated with an eluting solution and subsequently chromatographed by using the solvent system of *n*-BuOH-AcOH-H₂O (4:1:1 v/v). Each 15 g portion of the eluate collected was checked by PC, and the eluates were divided into five fractions (Fraction I~V). Fraction I (eluates No. 22~26), 354 mg of dried powder which consisted of Spot 1 and 2; Fraction II (eluates No. 27~38), 453 mg of Spot 1, 2 and 3; Fraction III (eluates No. 39~66), 829 mg, mainly of Spot 3 and small amounts of Spot 1 and 2; Fraction IV (eluates No. 67~110), 489 mg of mixture of Spot 2, 3 and substances of lower *R_f* values than Spot 3; Fraction V (eluates No. 111~200), 392 mg, mainly of the latter of Fraction IV. Fraction I was rechromatographed under the same conditions as mentioned above, except that the cellulose column of 4.5×50 cm was used and each 15 g portion was collected by the fraction collector.

Isolated Spot 1 (fractions No. 37~43) could not be crystallized, but its *R_f* values of PC and TLC with two solvent systems (*n*-BuOH:AcOH:H₂O=4:1:1, Phenol:H₂O=4:1 in NH₃ vapor) agreed with that of authentic alanine. The fraction (No. 44~55) was a mixture of Spot 1 and Spot 2. Another component of Fraction I was isolated purely after the fraction No. 56. Fractions of No. 56~60 were combined and evaporated to dryness and recrystallized from ethanol/water in yield of 54.3 mg and mp 230°C (dec.). The values of elementary analysis agreed closely with 2-methylserine (Found: C, 40.23; H, 7.66; N, 11.39.

Calcd. for C₄H₉NO₃: C, 40.33; H, 7.61; N, 11.76%).

5-Dichloromethyl-5-methylhydantoin (II) and its hydrolysis product. II, mp 238~41°C, *Anal.* Found: C, 30.26; H, 2.99; N, 14.28. Calcd. for C₅H₈N₂O₂Cl₂: C, 30.48; H, 3.08; N, 14.22%. NMR $\tau_{\text{DSS}}^{\text{D}_2\text{O}, \text{NaOD}}$: 8.50 (3H, s, -C-CH₃), 4.10 (1H, s, -C-CHCl₂). Fifteen grams of II was hydrolysed and desalted by the same procedure as described above. It was shown that the desalted solution of hydrolyzate consisted of only one ninhydrine positive substance. White and sweet powder (6.16 g) was obtained by adding ethanol to the concentrated solution and recrystallized from ethanol/water. It was sublimed and decomposed immediately above 265°C. Its *R_f* values of PC and TLC coincided with those of authentic alanine. *Anal.* Found: C, 40.32; H, 8.07; N, 15.67. Calcd. for C₃H₇NO₂: C, 40.44; H, 7.92; N, 15.72%. The yield of alanine from II was 90.4%.

5-Chloromethyl-5-ethylhydantoin (III), 5-(1-chloroethyl)-5-methylhydantoin (IV) and 5-trichloromethylhydantoin (V). III, IV and V were prepared by the partly modified Bucherer's method. Details were shown in the previous paper.¹⁾ 1-Chloro-2-butanone fraction, bp 137~147°C and 3-chloro-2-butanone fraction, by 114~118°C were obtained by the fractional distillation of the chlorinated 2-butanone mixture, and chloral hydrate was purchased. Each one of these carbonyl compounds, 1.2 times the molar quantity of potassium cyanide and 3~3.5 times the molar quantity of ammonium carbonate were allowed to react in the 75% ethanol at 60~65°C for 4~5 hr and in addition at 85°C another 1 hr. A reaction mixture was neutralized with conc. HCl and extracted with ethyl acetate. Hydantoin was obtained from the concentrated extract on cooling. The yields of the hydantoin were very poor in every case.

9) Toyo Cellulose Powder, 100~200 mesh (Yoyo Roshi Co., Ltd.) was used.

Results were as follows: III, mp 185~6°C, yield 13%. Found: C, 41.00; H, 5.09; N, 15.76. Calcd. for $C_6H_9N_2O_2Cl$: C, 40.80; H, 5.13; N, 15.86%.

IV, mp 231~2°C, yield 21%. Found: C, 41.00; H, 5.17; N, 16.01%. Calcd. for $C_6H_9N_2O_2Cl$: C, 40.80; H, 5.13; N, 15.86%. V (dihydrate),* mp 98~

100°C, yield 8%. Found: C, 18.81; H, 2.54; N, 11.09. Calcd. for $C_4H_3N_2O_2Cl_3 \cdot 2H_2O$: C, 18.95; H, 2.78; N, 11.05%. 100 mg of V was hydrolyzed in a solution of 1 M barium hydroxide. *R_f* values on TLC of the hydrolyzate which coincided with those of authentic glycine, were 0.29 and 0.35 in the solvent systems *n*-BuOH : AcOH : H₂O=4 : 1 : 2 and phenol : H₂O=4 : 1 (in NH₃ vapor), respectively.

* It was found that this compound was not a hydantoin but α , α -dichloroacetamide, and the reaction was now under reinvestigation.