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Chemistry of Amino Acids. V.[1] Studies on α-Alkyl-α-amino Acids. IX.[2] Mild Hydrolytic Ring Cleavage of Hydantoin Derivatives

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It was found that hydantoin nuclei (Ia—d) were easily hydrolysed with caustic alkali to give hydantoic acid derivatives (IIIa—c) by way of 3-tosylhydantoin derivatives (IIa—d). IIIa—c were further hydrolyzed to amino acids with diluted hydrochloric acid. The hydrolysis of IId with alkali did not furnish the hydantoic acid derivative IIId but gave N-tolylsulfonyl-2-amino-2-isobutyl-4-methylvaleramide VI, probably due to the steric effect.

Preparation of α-amino acids through hydantoins is well known and this route is called the Bücherer procedure.[4,5] The hydantoin ring is generally resistant to cleavage by acid or base, acid hydrolysis being particularly more difficult than an alkaline one. Therefore, alkaline hydrolysis of hydantoins to α-amino acids was preferred although the reaction conditions are considerably severe. For example, in acidic hydrolysis, hydantoins are usually refluxed in 6 N hydrochloric acid for 96 hours at 110° to give α-amino acids in good yield. However, threonine, serine and tryptophan which are unstable in the acidic condition were obtained in very poor yield, 9%, 4% and 0% respectively under similar reaction conditions.[6] On the other hand, under the alkaline conditions hydantoins are, in general, hydrolyzed to the corresponding amino acids in good yield at a temperature of 110° for 24 hours in aqueous 0.1 N sodium hydroxide solution.[6] Many modifications of the alkaline hydrolysis procedure have been introduced for the purpose of increasing the relatively poor yield and shortening the reaction time. Sometimes alkali hydrolysis is performed with aqueous 20% barium hydroxide solution[7] in an autoclave under pressure of 50—60 lbs/in^2 for one to two hours or 15—20 lbs/in^2 for 15 hours in a steam bath, a longer time being required for hydrolysis at atmospheric pressure.

It has been recognized that 5,5-dialkylhydantoins are much more resistant to hydrolysis than 5-monoalkylhydantoins under the foregoing alkaline conditions. 5,5-Dimethyl,[8] 5-ethyl-5-methyl-,[8] 5-methyl-5-pentyl-,[8] 5,5-diisopropyl-[8] and 5,5-diisobutyl-hydantoin[8] were hydrolyzed to the corresponding α-alkyl-α-amino acids in 80%, 70%, 51%, 0% and 11% yield respectively with barium hydroxide under the pressure of 50—60 lbs/in^2 and hydrolysis of 5-ethyl-5-methylhydantoin with aqueous barium hydroxide under an atmospheric pressure required a reflux for 60 hours.[9]

An attempt has been made to establish a milder cleavage procedure of hydantoin derivatives, especially, 5,5-disubstituted hydantoins. At the initiation of the present work, it

1) Part IV: *Chem. Pharm. Bull.* (Tokyo), **16**, (1968).
2) Part VIII: *Chem. Pharm. Bull.* (Tokyo), in press.
3) Location: *Bunkyo-ku, Tokyo.*
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5) H.T. Bücherer and V.A. Lieb, *J. Prakt. Chem.*, **141**, 5 (1934).
6) G.R. Stark and D.G. Smyth, *J. Biol. Chem.*, **238**, 214 (1963).
7) J.E. Livak, S.C. Clemson, and E.C. Britton (to Dow Chemical Co.), U.S. Patent 2527366 (Oct. 24, 1950).
8) S.D. Upham and O.C. Dermer, *J. Org. Chem.*, **22**, 799 (1957).
9) Our unpublished data.

was posited that if a tolylsulfonyl group, which is electron attractive, could be introduced at position N^3 of a hydantoin nucleus, the hydantoin nucleus might be hydrolyzed more easily than a hydantoin ring without such a group, as shown in Chart 1.

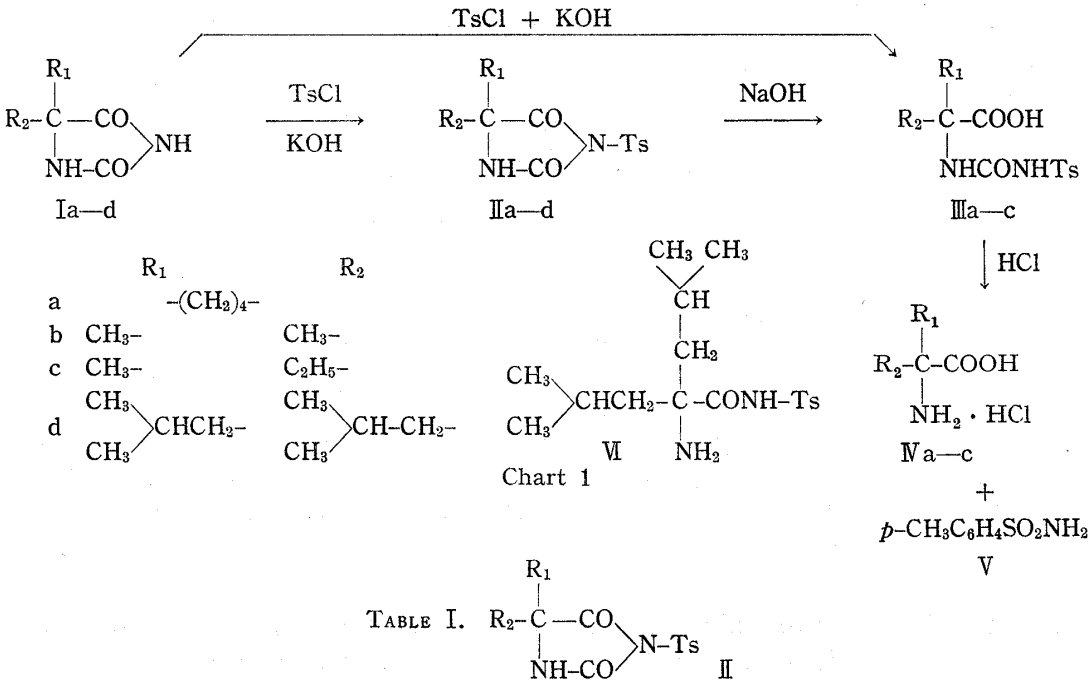

Chart 1

TABLE I.

	R_1	R_2	mp (°C)	yield (%)	Formula	Analysis (%) Calcd. C	H	N	Found C	H	N
a		$-(-CH_2)_4-$	223—225	63.7	$C_{14}H_{16}O_4N_2S$	54.54	5.23	9.19	54.25	5.39	8.92
b	CH_3	CH_3	146—147	43.2	$C_{12}H_{14}O_4N_2S$	51.06	5.00	9.93	50.98	4.98	9.87
c	CH_3	C_2H_5	122—123	48.5	$C_{13}H_{16}O_4N_2S$	52.70	5.44	9.46	52.88	5.59	9.07
d	$(CH_3)_2CHCH_2-$	$(CH_3)_2CHCH_2-$	175—176	53.2	$C_{18}H_{26}O_4N_2S$	59.00	7.15	7.65	59.18	7.08	7.59

Tosylation of spiro[cyclopentane-1,5′-hydantoin] (Ia) was first undertaken under various conditions as a model compound. Several bases were used as condensing agents. When strong bases, such as caustic alkali and triethylamine, were used as condensing agents, IIa was obtained in a moderate yield. However, when sodium hydride was employed in anhyd. dioxane the yield was unexpectedly bad, and use of a weak base produced a poor yield. It was found that when potassium hydroxide was used in aqueous acetone, the yield was best. Accordingly, this procedure was employed for preparing varoius 3-tosylhydantoins (IIa—d). The properties and analytical data of II are shown in Table I.

The structure of II was demonstrated by leading it to *p*-toluenesulfonamide (V) as described in the following part.

When 3-tosylhydantoins II thus obtained were treated with dilute aqueous caustic alkali under mild conditions, it was found, as expected, that ring opening of II readily took place to afford hydantoic acid derivatives III in good yield. For example, treatment of IIa with N NaOH at 3—4° for 3.5 hours or with 0.1 N NaOH at 60—65° for 7 hours gave hydantoic acid IIIa in 69.5% and 76% yield respectively. Moreover, hydantoic acids IIIa—c were also directly prepared by treatment of hydantoin Ia—c with tosyl chloride in aqueous caustic alkaline solution under mild reaction conditions. IIIa, IIIb and IIIc were obtained from

Ia, Ib and Ic in 44%, 33% and 48% respectively without separating II. Table II presents the analytical and preparative data of IIIa—c from Ia—c directly. In these cases, it is supposed that the reaction proceeded through the tosylation of I and subsequent hydrolysis of II. Surprisingly the hydrolysis of IId did not give the expected product IIId, but gave N-tosyl-2-amino-2-isobutyl-4-methylvaleramide (VI) in good yield. This result was probably due to the steric effect of the diisobutyl group.

TABLE II. $R_2-\underset{\displaystyle NH\cdot CONHTs}{\overset{\displaystyle R_1}{\overset{|}{\underset{|}{C}}}}-COOH$ III

	R_1	R_2	mp (°C)	Yield (%)	Formula	Analysis (%) Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
a	$-(CH_2)_4-$		130—130.5	43.8	$C_{14}H_{18}O_5N_2S$	51.37	5.81	8.56	51.51	6.00	8.43
b	CH_3	CH_3	142—142.5	32.5	$C_{12}H_{16}O_5N_2S$	48.00	5.37	9.34	48.11	5.51	9.51
c	CH_3	C_2H_5	137.5—138	48.2	$C_{13}H_{18}O_5N_2S$	49.68	5.77	8.91	49.86	5.46	8.68

Yields are based on I.

Hydrolysis of IIIa—c to amino acids was carried out in quantitative yield by a reflux of IIIa—c in 10% hydrochloric acid for 30 to 60 minutes. Amino acid hydrochlorides IVa—c and by-product, *p*-toluensulfonamide V, were easily separated according to their solubility in acidic solution. However, hydrolysis of IIIa—c in 2 N sodium hydroxide was unsatisfactory, and the starting material was recovered even after a reflux of 15 hours. IVa—c were, respectively, identified with the authentic samples prepared by the other route in a comparison of their IR spectra.

Experimental[10]

Tosylation of Hydantoins I

General Procedure——To a solution of hydantoin (1 mole) in acetone were added N KOH and a solution of TsCl (1.2—1.5 moles) in acetone, alternately, under ice cooling or at 25—30°. In this process the reaction mixture was kept alkaline, and was stirred for several hours under ice cooling or at 25—30°, adjusting pH to 9—10 by adding N KOH. The filtration of separated colorless crystals gave II which was purified by recrystallization. When II did not crystallize out, it was extracted with AcOEt from the reaction mixture, and purified by silica gel column chromatography.

1) **3′-Tosylspiro[cyclopentane-1,5′-hydantoin] (IIa)**——a) KOH in aq. acetone. To a solution of Ia (1.0 g, 0.0065 mole) in acetone (20 ml) was added a solution of TsCl (2.5 g, 0.0130 mole) in acetone (10 ml) and N KOH (28 ml) alternately dropwise. Adjusting the pH at 9—10, the reaction mixture was stirred for 9 hr at 25—30°. The filtration of separated crystals gave IIa (0.68 g), the evaporation of acetone from the filtrate gave the second crystals of IIa (0.36 g) and further the acidification of the filtrate with AcOH also afforded the additional IIa (0.17 g). Total yield of IIa was 1.21 g (63.7%). Recrystallization from EtOH–benzene yield colorless leaves mp 223—225°. IR ν_{max}^{KBr} cm^{-1}: 3380 (ν_{NH}), 1796, 1755 (hydantoin CO), 1380, 1176 (ν_{SO_2}), 820 (aromatic).

b) $(Et)_3N$ in acetone. To a solution of Ia (1.0 g, 0.0065 mole) in acetone (20 ml) were added $(Et)_3N$ (3.3 g, 0.0325 mole) and a solution of TsCl (1.9 g, 0.0096 mole) in acetone (10 ml). The reaction mixture was then stirred for 9 hr at 45—55° and refluxed for 5 hr. After cooling, the precipitated $N(Et)_3HCl$ was filtered off. The filtrate was concentrated to dryness *in vacuo* and H_2O was added to the residue. The separated yellow-brown crystals were recrystallized from EtOH–acetone to give IIa (0.85 g, 44.7%).

2) **3-Tosyl-5,5-dimethylhydantoin (IIb)**——TsCl (1.8 g, 0.00737 mole) dissolved in acetone (3 ml) was added to a solution of Ib (1.0 g, 0.00781 mole) in N KOH (8 ml) and stirred for 1 hr under ice cooling.

10) No melting points are corrected. IR spectra were measured with a Spectrophotometer, Model. DS-301 equipped with NaCl optics.

Additional N KOH (6.5 ml) was added dropwise for 6 hr at 35°. The separated crystals were filtered to give IIb (0.95 g, 43.2%), which was recrystallized from ether–$CHCl_3$, as colorless needles, mp 146—147°. IR ν_{max}: 3250 (ν_{NH}), 1793, 1755 ($\nu_{C=O}$), 1600 (aromatic), 1382 (ν_{SO_2}), 1176 (ν_{SO_2}), 812 (aromatic).

3) **3-Tosyl-5-ethyl-5-methylhydantoin (IIc)**——IIc was prepared from Ic by the same reaction condition described in the general procedure. The oily layer of the reaction mixture solidified after standing overnight. These crystals were collected to give IIc which was recrystallized from benzene–Et_2O as colorless prisms, yield 48.5%, mp 122—123°. IR ν_{max}^{KBr} cm^{-1}: 3240 (ν_{NH}), 1797, 1751 (hydantoin CO), 1395, 1180 (ν_{SO_2}), 810 (aromatic).

4) **3-Tosyl-5,5-diisobutylhydantoin (IId)**——IId was prepared according to the general procedure in 53.2% yield as colorless needles, mp 175—176° (EtOH–ether). IR ν_{max}^{KBr} cm^{-1}: 3425 (ν_{NH}), 1795, 1761, 1740 (CO), 1600 (aromatic), 1387, 1178 (ν_{SO_2}), 812 (aromatic).

Cleavage of 3-Tosylhydantoins with Alkali

1-(3-tosylureido)-1-cyclopentanecarboxylic Aicd (IIIa)——A solution of IIa (0.20 g, 0.00065 mole) in N NaOH (10 ml) was stirred under ice cooling (3—4°) for 3.5 hr. The reaction mixture was acidified with HCl and then the colorless crystals separated were filtered to give IIIa (0.14 g, y. 69.5%). Colorless prisms, mp 130—130.5° (Benzene–EtOH). A mixed melting point with a sample prepared in the following section, was undepressed, and IR spectra of these two samples were superimposable.

Direct Formation of Hydantoic Acid Derivatives (III) from Hydrantoin (I)

1) **1-(3-Tosylureido)-1-cyclopentanecarboxylic Acid (IIIa)**——To a solution of Ia (2.0 g, 0.013 mole) in N KOH (14 ml) were added a solution of TsCl (3.0 g, 0.0156 mole) in acetone (7 ml) and N KOH (16.5 ml) alternately to keep the reaction mixture alkaline, and the whole was stirred for 5 hr at 35°. To the reaction mixture was added further N KOH (14 ml) and stirring was continued for an additional 2 hr at 60°. The reaction mixture was slightly acidified to separate out crystals of the starting material. The filtrate was again acidified with 10% HCl, and the white crystals precipitated were filtered to give IIIa (1.85 g, 43.8%) which was recrystallized from benzene–EtOH as colorless prisms, mp 130—130.5°. IR ν_{max}^{KBr} cm^{-1}: 2600 (broad), 1710 (COOH), 1655 (ureidocarbonyl), 1344 (ν_{SO_2}), 1163 (ν_{SO_2}).

2) **2,2-Dimethyl-5-tosylhydantoic Acid (IIIb)**——IIb was prepared according to the same procedure described above. Without separating IIb, additional N KOH (10 ml) was added to the tosylated mixture and further stirring was continued for 3.5 hr at 40—45°. The same working up as above gave IIIb (0.38 g, 32.5%) which was recrystallized from acetone–$CHCl_3$ as colorless needles, mp 142—142.5°. IR ν_{max}^{KBr} cm^{-1}: 2500 (broad), 1695 (COOH), 1650 (ureido carbonyl), 1352 (ν_{SO_2}), 1162 (ν_{SO_2}).

2-Ethyl-2-methyl-5-tosylhydantoic Acid (IIIc)——IIIc was prepared from Ic directly according to the same method as IIIa from Ia, yield 48.2%. Recrystallization from acetone–$CHCl_3$ gave pure IIIc, colorless prisms, mp 137.5—138°. IR ν_{max}^{KBr} cm^{-1}: 2500 (broad), 1693 (COOH), 1648 (ureido carbonyl), 1360 (ν_{SO_2}), 1165 (ν_{SO_2}).

Amino Acid Hydrochlorides (IV)

General Procedure——III was refluxed with 10% HCl for an hour. After standing overnight, the separated *p*-toluenesulfonamide (V) (mp 137—138°) was filtered off and identified with an authentic sample by comparison of their IR spectra and mixed melting points. The filtrate was concentrated to dryness *in vacuo* to give IV which was then purified by recrystallization from EtOH–ether. All the amino acid hydrochlorides (IV) thus obtained were identified by similarity in IR spectra as well as by mixed melting points with the authentic samples (IVa,[11] IVb,[4] IVc[4]), prepared by another methods.

N-Tolysulfonyl-2-amino-2-isobutyl-4-methylvaleramide (VI)——IId (1.0 g, 0.00273 mole) was heated with N KOH (27 ml) at 70—80° for 4.0 hr. The reaction mixture was neutralized with AcOH, and the separated colorless crystals were filtered to give VI, which was recrystallized from EtOH–acetone as white leaves 0.80 g (y. 86.9%), mp 256—257°, IR ν_{max}^{KBr} cm^{-1}: 3200 (ν_{NH}), 1601, 1580 (amide carbonyl), 1330, 1151 (ν_{SO_2}), 812 (aromatic). *Anal.* Calcd. for $C_{17}H_{28}O_3H_2S$: C, 59.98; H, 8.29; N, 8.23. Found: C, 59.67; H, 8.27; N, 8.63. Hydrochloride white prisms, mp 261° (decomp.). IR ν_{max}^{KBr} cm^{-1}: 2800—2400 broad (ν_{NH}^{+}), 1701 (amide carbonyl), 1600 (aromatic), 1345, 1174 (ν_{SO_2}), 810 (aromatic). *Anal.* Calcd. for $C_{17}H_{29}O_3N_2SCl$: C, 54.18; H, 7.70; N, 7.43. Found: C, 53.98; H, 7.85; N, 7.17.

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