

Organic Syntheses in Non-Aqueous Solutions. II

The Alkylation of Glycine Derivatives in Liquid Ammonia

Part I. Benzylation of Hydantoin in Liquid Ammonia

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Synopsis

The metalation of hydantoin and thiohydantoin has been conducted in liquid ammonia and then the reactions between the produced sodium compounds of hydantoin and thiohydantoin and benzyl chloride have been studied.

I. Introduction

Hydantoin, $\text{CH}_2 \begin{matrix} \text{NH-CO} \\ | \\ \text{CO-NH} \end{matrix}$, glycine anhydride, $\text{CH}_2 \begin{matrix} \text{NH-CO} \\ \diagup \quad \diagdown \\ \text{CO-NH} \end{matrix} \text{CH}_2$, and hippuric acid, $\text{C}_6\text{H}_5\text{-CO-NH-CH}_2\text{COOH}$, etc. have a glycylic residue, $-\text{NH-CH}_2\text{-CO-}$, respectively, the Perkin condensation between the active methylene in the residue and an aldehyde is easily conducted. Utilizing the reaction, the syntheses of higher α -amino acids using hydantoin, glycine anhydride and hippuric acid have been studied by Wheeler and Hoffman⁽¹⁾, Sasaki⁽²⁾, and Erlenmeyer⁽³⁾, etc. These Perkin condensations are caused by the condensation of carbonyl compounds with carbanion produced by deprotonization of the active methylene group. If the alkylation is occurred between an alkyl halide and an organometallic compound, obtained by the metalation of the above active methylene group using a liquid ammonia solution of an alkali metal as a strong base for causing the deprotonization, α -amino acids are assumed to be easily prepared by omitting the reduction process comparing with the Perkin condensation. However, there is a hydrogen atom not only in the methylene radical ($-\text{CH}_2-$) but also in the imino group ($-\text{NH-}$), which is in the state to be deprotonized and has a possibility to receive the action of metalation, for clearing up the problem, the possibility of alkylation of these compounds has been studied.

In the first report, the metalation and benzylation of hydantoin have been dealt with.

Experimental Method

All the reaction using liquid ammonia has been conducted at room temperature using a pressure-proof glass reaction tube for observing the reaction state from

(1) H. J. Wheeler and C. Hoffman, *Amer. Chem. J.*, **45**, (1911) 368.

(2) T. Sasaki, *Ber.*, **54**, (1921) 163.

(3) E. Erlenmeyer, *Ann.*, **275**, (1893) 1.

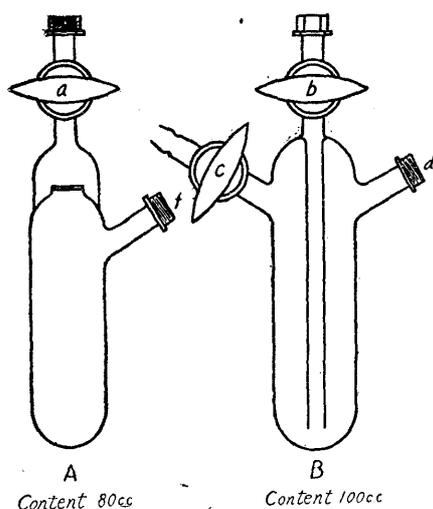


Fig. 1

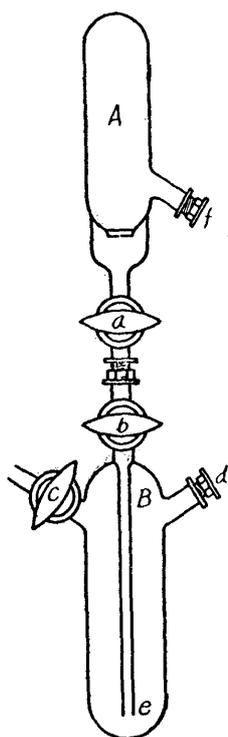


Fig. 2

the outside. As the metalation and alkylation, which will be conducted hereafter, will be operated using the reaction tube of the system or a properly improved one, a detailed operating process will be described here. Small pieces of metallic sodium are thrown into A-reaction tube (content: 80 cc) and liquid ammonia is condensed in the reaction tube after closing it with a blind bagnet, thereby a liquid ammonia solution of sodium is obtained. In the case of preparing a liquid ammonia solution of KNH_2 , small pieces of metallic potassium are thrown into the A-reaction tube with a few pieces of iron rust as a catalyst. By cooling the tube, potassium is dissolved in liquid ammonia producing KNH_2 as a transparent light yellow solution after a few hours. By the same process, a liquid ammonia solution of an organic compound to be reacted was prepared in the B-reaction tube (content: 100~120 cc).^(Note 1) The two reaction tubes of A and B were connected as shown in Fig. 2. The B-tube was cooled with ice. After slightly and gradually opening cock *c*,^(Note 2) cocks *a* and *b* were opened, by which the content of the A-tube was gradually added into the B-tube under pressure. At *e* part of the B-tube, metalation smoothly proceeded as the two solutions reacted each other. In the case of sodium-ammonia solution, a deep blue color peculiar to the solution quickly disappeared at near *e* part, which showed the progress of metalation. By observing the decolorizing state, the end of the reaction could be able to determine.

After the completion of metalation, the A-tube was taken off from the B-tube, which was then cooled at below -33° (boiling point of ammonia). An alkylating agent such as alkyl halide was then added into the tube through the side tube *d* and closed with a blind bagnet. The cock *c* was also closed and the whole was brought to room temperature and was shaken or set for a definite time. After the reaction was completed, the cock *e* was gradually opened and ammonia was evaporated to dryness. Lastly, the content was dried by evacuating with a vacuum pump and the residue was minutely examined.

Note 1. When a liquid ammonia solution of NaNH_2 is used, NaNH_2 solution prepared in the B-tube because it is sparingly soluble in liquid ammonia, and a liquid ammonia solution of an organic compound is prepared in the A-tube for the reaction.

Note 2. In this case, the cock *c* is gradually and slightly opened for reducing the additional pressure due to hydrogen which is always evolved in the case of metalation with a liquid ammonia solution of sodium according to the following reaction: $\text{Na} + \text{RH} \rightarrow \text{Na}^+ + \text{R}^- + \frac{1}{2}\text{H}_2$. When the metalation is conducted with KNH_2 or NaNH_2 , no hydrogen is evolved, there is no need to open the cock in the latter case.

II. Experimental Materials

Hydantoin (I) was prepared from glycine ethylester hydrochloride and NaOCN according to Harris and Weiss⁽⁴⁾, white crystals, m. p. 218°.

2-Thiohydantoin (II) was prepared from acetylglycine ethylester hydrochloride and KSCN according to Johnson and Nicolet⁽⁵⁾, yellow plates, m. p. 223~5°.

Benzyl chloride was prepared by purifying a commercial product of the first grade, by the treatment with potassium carbonate, b. p. 175~7°.

III. Experiments

(i) Metalation and benzylation of hydantoin by a liquid ammonia solution of metallic sodium

Two hundredth mole (0.46 g) of metallic sodium was dissolved in 30 cc of liquid ammonia in the A-reaction tube, while 2 g (0.02 mole) of hydantoin were dissolved in 30 cc of liquid ammonia in the B-reaction tube. By mixing the two solutions, metalation was caused quickly precipitating white crystals, as the produced sodium compound being insoluble in liquid ammonia. After one hour, 2.8 g (0.022 mole) of benzyl chloride were added into the reaction tube and shaken. Within a few hours, the crystals disappeared, resulting a clear solution. After 20 hours' setting at room temperature, ammonia was evaporated off and the residue was extracted with 50 cc of hot alcohol, separating off the sodium chloride produced. By cooling in an ice box, the alcoholic solution gave 1 g of crystals, which was confirmed to be hydantoin, from the melting point, 213~5°, of recrystallised product from hot water and the mixed-melting point test with the starting material, hydantoin. A compound was obtained from the alcoholic mother liquor, which seemed to be benzylamine, confirmation of which would be however conducted in the next experiment.

(ii) Metalation and benzylation of hydantoin by a liquid ammonia solution of KNH_2

One gram (0.025 mole) of metallic potassium was dissolved in liquid ammonia in the A-reaction tube, forming KNH_2 in the presence of an iron catalyst in the solution. Two and half grams (0.025 mole) of hydantoin were dissolved in 40 cc of

(4) C. Harris and M. Weiss, *Ber.*, **33**, (1900) 2418.

(5) T. B. Johnson and B. H. Nicolet, *J. Amer. Chem. Soc.*, **33**, (1911) 1976.

liquid ammonia in the B-reaction tube, into which the solution in the A-tube was gradually added. The metalation vigorously occurred by which potassium compound of hydantoin became pasty, to which 3.5 g (0.028 mole) of benzyl chloride were added after one hour. After the lapse of one hour, the pasty precipitate disappeared and crystals of potassium chloride were separated out amounting to about 1.7 grams. After 24 hours setting at room temperature, the crystals were filtered off. The precipitate obtained by evaporating off ammonia was washed several times with ether. The ether-insoluble residue was recrystallised from hot water as white crystals, m. p. $215\sim 8^\circ$, which were proved to be the material hydantoin. The ethereal solution gave two compounds by distillation *in vacuo*, one, b. p. $41\sim 42^\circ/2$ mmHg and n_D^{20} 1.5440, was proved to be benzylamine, yield, 2 g, and the other, b. p. $107\sim 8^\circ/2$ mmHg and n_D^{20} 1.5678, was dibenzylamine, yield, 0.6 g.

(iii) Metalation of hydantoin by means of a liquid ammonia solution of metallic sodium and benzylation in an ethereal solution

Hydantoin-sodium compound was prepared from 2 g (0.03 mole) of hydantoin and 0.46 g (0.02 mole) of metallic sodium in liquid ammonia. After evaporating off liquid ammonia, 2.8 g (0.02 mole) of benzyl chloride and 100 cc of absolute ether were added to the residue and benzylation was conducted at $35\sim 40^\circ$ for 6 hours. After the reaction, the ethereal solution was separated from the residue, from which 2 g of unreacted benzyl chloride was recovered. The residue was decomposed with water, neutralised with hydrochloric acid, from which 1 g of hydantoin was recovered. The residue obtained after the reaction was hydantoin-sodium compound.

(iv) Metalation of hydantoin by means of a liquid ammonia solution of potassium and benzylation in benzyl chloride

Hydantoin-potassium compound was prepared from 2 g (0.02 mole) of hydantoin and 0.8 g (0.02 mole) of metallic potassium in liquid ammonia, completely removing off the solvent, the potassium compound was reacted with 40 cc of benzyl chloride at 100° for 5 hours and the product was extracted with ether. Unreacted benzyl chloride was recovered from the ethereal solution and 1 g of hydantoin from the insoluble residue as in the case of (iii).

(v) Metalation and benzylation of 2-thiohydantoin by means of a liquid ammonia solution of metallic sodium

Two grams (0.02 mole) of 2-thiohydantoin were dissolved in 40 cc of liquid ammonia to a brown solution, to which a solution of 0.43 g (0.02 mole) of metallic sodium in 30 cc of liquid ammonia was added. By the metalation white crystals were precipitated as in the case of hydantoin. By mixing and shaking with 2.4 g (0.02 mole) of benzyl chloride, the crystals disappeared. After 20 hours setting at room temperature, ammonia was evaporated off, leaving a brown residue, from which sodium chloride was separated by the treatment of alcohol. By distilling off alcohol, a blackish brown colored oily substance was obtained, which then gave, on vacuum distillation, a small amount of mercaptane, b. p. $60\sim 65^\circ/2$ mmHg. n_D^{20} 1.5475, a small amount of light brown colored oily substance boiling at $170\sim 190^\circ$

2 mmHg, and a black decomposition product.

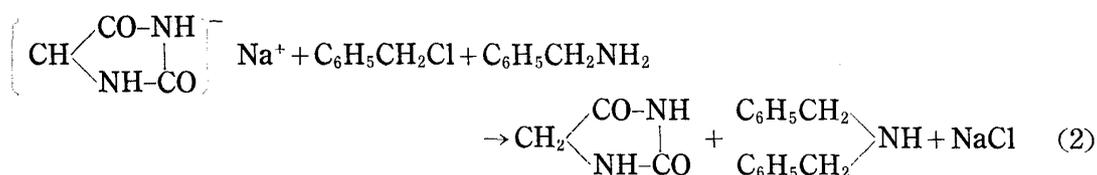
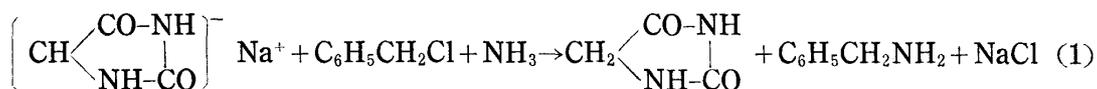
(vi) Metalation and benzylation of 2-thiohydantoin by means of a liquid ammonia solution of KNH_2

Thiohydantoin-potassium compound was prepared from 2 g (0.02 mole) of thiohydantoin and KNH_2 , prepared from 1 g (0.025 mole) of metallic potassium in liquid ammonia in the form of white crystals, which disappeared and crystals of potassium chloride were separated out by the reaction with 2.4 g (0.02 mole) of benzyl chloride. After 20 hours, ammonia was evaporated off, obtaining potassium chloride and a brown colored oily substance as in the case of (v).

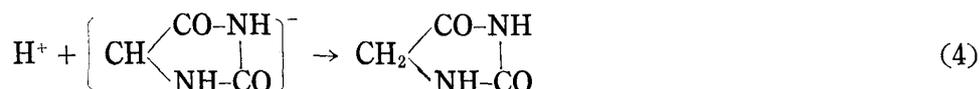
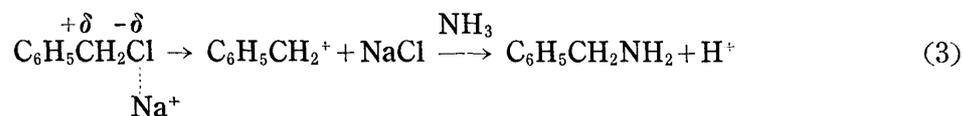
IV. Discussion

By the above experiments, it was found that hydantoin and thiohydantoin gave alkali metal compounds, insoluble in liquid ammonia, by the metalation with metallic sodium, potassium, and KNH_2 in liquid ammonia. In the above case, the reaction was conducted in the equal mole ratio. When the mole ratio of hydantoin and metal was 1:2, metalation was also smoothly conducted, which proved the presence of at least more than two active hydrogens in hydantoin.

In the experiments (i) and (ii), the metal compound gave hydantoin, benzylamine, dibenzylamine and an inorganic salt by the benzylation in liquid ammonia, the reactions were assumed as follows: (Note 3)



As stated above, only the metallic compound of hydantoin was decomposed into hydantoin without accepting benzylation differing from metallic compounds of glycine anhydride and hippuramide, which will be described in the next report. The reaction mechanism is assumed to be as follows, essentially differing from the above two compounds, details of which will be described in the next report.



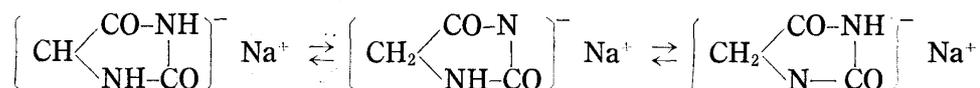
As in the cases of (iii) and (iv), a metallic compound of hydantoin does not react with benzyl chloride in an organic solvent except liquid ammonia. The cause is assumed in two ways; (1) the ionic dissociation of a metal compound of hydantoin, which is necessary in the ionic reaction like the reaction (3), will be

difficult to occur in an organic solvent such as ether or benzyl chloride; or (2) as the reaction products, hydantoin and an inorganic salt, are insoluble in these solvents, further reaction velocity is very slow, though the reaction (3) has already occurred.

From this point of view, the advantageous fact of liquid ammonia as a solvent for alkylation of a metallic organic compound will be understood and moreover gives a suggestion for alkylation in liquid ammonia.

In the cases of metallic compounds of thiohydantoin in (v) and (vi), thiohydantoin has not been isolated by benzylation, but the decomposition perhaps proceeded to benzylmercaptane through thiohydantoin, as the mercaptane was approved. Komatsu⁽⁶⁾ reported that thiohydantoin-potassium compound gave three kinds of methylated isomers by methylation. In the case of benzylation of the metallic compound, corresponding 3-benzyl-2-thiohydantoin and 5-benzyl-2-thiohydantoin have not been obtained. Therefore, further investigations of the oily substances obtained from the residue treated with alcohol in the experiments (v) and (vi) have not been conducted.

(Note 3) Hydantoin-Na compound should be expressed as follows. i. e., Na⁺ should not be thought to be combined with a definite carbon or nitrogen:



Conclusion

The metalations of hydantoin and thiohydantoin by means of sodium, potassium, and potassium amide are easily conducted in liquid ammonia, producing white crystalline precipitates, which are insoluble in the solvent. The metalation in this case is possible to react with at least more than two moles of the metal.

Hydantoin-metal compounds react with benzyl chloride in liquid ammonia, producing hydantoin and the group of benzylamines. The benzylation, however, does not occur in an organic solvent except liquid ammonia.

In the benzylation in liquid ammonia, thiohydantoin-metal compounds seem to decompose into benzyl mercaptane through thiohydantoin.

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(6) S. Komatsu, Mem. Coll. Sci. and Eng., Kyoto Imp. Univ. 2 (1911), No. 1, 1.