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Organic Synthetic Chemistry in Liquid Ammonia. II

Etherification of *d*-Mannitol

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Synopsis

d-Mannitol is metallized by reacting with metallic potassium and potassium hydroxide in liquid ammonia, producing di- and mono-substitution products. These organometallic compounds form di-benzyl ether, respectively, reacting with benzyl chloride.

I. Introduction

Many methods⁽¹⁾⁻⁽¹⁰⁾ have been attempted on the etherification of comparatively active hydroxyl radical of hexahydric alcohols, such as *d*-mannitol. Attempts to apply the so-called Williamson's synthetic method to carbohydrates in liquid ammonia, such as the works of Muskat⁽¹¹⁾ or Amagasa⁽¹²⁾, etc. have been rarely done⁽¹³⁾. The present authors have prepared metallic compound of *d*-mannitol corresponding to alkali alcoholate in the above synthetic method using alkali metal and alkali hydroxide in liquid ammonia, from which *d*-mannitol benzyl ether was obtained by reacting with benzyl halide.

II. Experimental part

1. Reaction between *d*-mannitol and alkali metals in liquid ammonia

Three grams (about 1/60 mole) of *d*-mannitol (m.p. 164-5°), purified by recrystallizing a commercial product from dilute alcohol, were put in a pressure bottle shown in Fig. 1, in which (a) part was connected and (d) part closed. Twenty cc of dehydrated and redistilled liquid ammonia were introduced into the bottle through (b) part. *d*-Mannitol was quickly dissolved. (According to the method of Shimo and Kaminishi⁽¹⁴⁾, the solubility of *d*-mannitol in 100 grams of

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- (2) Nichols and Yanovsky, *J. Am. Chem. Soc.*, **67** (1945), 46.
- (3) Haskins, Hann and Hudson, *J. Am. Chem. Soc.*, **65** (1943), 70.
- (4) Bua and Tibaldai, *Farm. sci. e tec. (Pavia)*, **6** (1951), 448; *C. A.*, **46** (1952), 8004.
- (5) Irvine and Paterson, *J. Chem. Soc.*, (1914), 899; 915.
- (6) Wiggins, *J. Chem. Soc.*, (1946), 384.
- (7) Wrigley and Yanovsky, *J. Am. Chem. Soc.*, **70** (1948), 2194.
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- (9) Chapman and Owen, *J. Chem. Soc.*, (1950), 591.
- (10) Sweeney, Wiggins and Wood, *J. Chem. Soc.*, (1952), 37.
- (11) Muskat, *J. Am. Chem. Soc.*, **56** (1934), 693; 2449.
- (12) Amagasa, Onikura and Hori, *J. Soc. Chem. Ind. Japan*, **52** (1949), 2.
- (13) Soltzberg, *U. S. Pat.*, 2,234,200, Mar. 11; *C. A.*, **35** (1941), 3648.
- (14) Shimo and Kaminishi, *Bull. Chem. Res. Inst. Non-Aq. Solns.*, **1** (1951), 51.

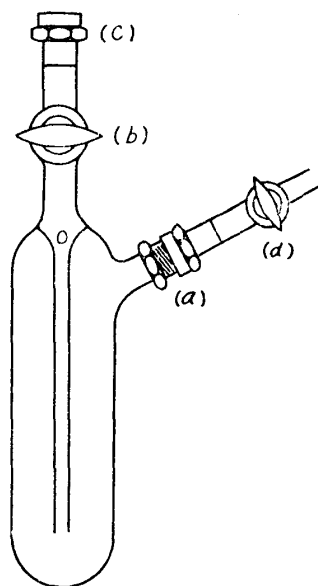


Fig. 1

liquid ammonia was 172 grams at 0°, 182 grams at 20° and 201 grams at 30°). An alkali metal of an equivalent mole to *d*-mannitol was dissolved in liquid ammonia in another pressure bottle having a filter plate, the volume of which being 60 cc. It was connected to the first bottle by the (c) part. Under cooling and frequent shaking, the liquid ammonia solution of the alkali metal was added to the liquid ammonia solution of *d*-mannitol drop by drop through the dropping pipe. The mixed solution foamed and the special deep blue color of alkali metal-liquid ammonia solution quickly disappeared. At the time about one third mole of the alkali metal to one mole of *d*-mannitol reacted each other, white precipitate began to appear.

During the reaction evolved gas was set free at times through the (d) part under protection of soda lime for reducing the increasing pressure. When all the alkali metal solution was added, it was kept at room temperature until the color of the solution was completely decolorized. Then the upper clear solution was taken into a third pressure bottle from the (c) part through filter paper. The reaction product was washed twice with 50 cc of dehydrated and redistilled liquid ammonia and freed from ammonia under reduced pressure protecting from moisture. The (a) part was removed and the product was wetted with dehydrated benzene, put in a desiccator containing sulphuric acid, freed from benzene and ammonia, and dried as the sample.

After confirming the absence of free ammonia with a test paper wetted with phenolphthalein, the sample was used for the determination of alkali and the etherification.

Two or three tenths gram of the reaction product was titrated with a decinormal hydrochloric acid using methyl orange as an indicator, the result being shown in Table 1.

Table 1

Kinds of alkali metals	Mole ratio in the reaction	Mean percentages of the alkali metals in the reaction products	Mean mole ratio in the substitution metal/ <i>d</i> -mannitol
Li	1	7.71	2.1
	2	8.21	2.3
	3	10.58	3.0
Na	1	18.96	1.8
	1	20.49	2.0
K	1	28.31	1.8
	1	28.90	1.8
(KNH ₂ { Ca	1	26.65	1.7)
	0.5	17.83	0.9)
	1	20.61	1.1)

By mixing the two components at room temperature, di-substitution compounds of lithium, sodium and potassium were obtained. When lithium was used as the alkali metal, 1.7 grams of *d*-mannitol were recovered from the upper clear solution, which corresponded to about one half of the used *d*-mannitol and suggested the production of di-substitution compounds. When calcium was used, di-substitution compound was also obtained. These facts suggested that two hydroxyl radicals were attacked in the reaction. Chablay⁽¹⁵⁾⁽¹⁶⁾ and Schmid and Becker⁽¹⁷⁾ obtained mono-substitution compounds of sodium and potassium, which were different from the author's case. In the case of sodium- and potassium-substitution compounds, the decoloration during the reaction was not smooth and the reaction products were sticky and hygroscopic. The activity difference between the hydroxyl radicals of *d*-mannitol was assumed from the fact that the reaction velocity of the third mole of lithium suddenly decreased taking a few hours, although the former reaction with the first and second mole of it's metal took place quickly and smoothly.

2. Reaction between *d*-mannitol and alkali hydroxides in liquid ammonia

Sodium alcoholate reacted with *d*-mannitol in dehydrated hot alcohol, producing a metallic compound⁽¹⁸⁾. Shimo and Asami⁽¹⁹⁾ have found that the substitution of hydrogen atom of active methylene with alkali metals in liquid ammonia was also conducted with alkali hydroxides. Then, by the condensation with an alkyl halide, C-alkyl compounds of malonic acid derivative and cyano-acetic acid derivative have been prepared. So also N-alkyl compound of glycine derivative was obtained by the same process. The present authors have perceived the production of organometallic compound by the reaction between potassium alcoholate and *d*-mannitol in liquid ammonia at room temperature. Further, the present authors have perceived the formation of two kinds of organometallic compounds by the mutual reaction between an alcohol solution of potassium hydroxide and a liquid ammonia solution of *d*-mannitol at room temperature. At the above article, the reaction between an alkali hydroxide and *d*-mannitol in liquid ammonia at room temperature has been tried as a contribution to the O-alkylation.

Three grams (about 1/60 mole) of *d*-mannitol (m. p. 164-5°), recrystallized from dilute alcohol, were mixed with an equivalent mole of commercial alkali hydroxide in a pressure bottle shown in Fig. 2, to which 50 cc of distilled liquid ammonia were added. *d*-Mannitol

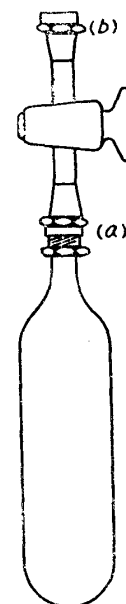


Fig. 2

(15) Chablay, C. r., **140** (1905), 1396.

(16) Chablay, A. ch., [9] **8** (1917), 164.

(17) Schmid and Becker, Ber., **58** (1925), 1966.

(18) Forcrand, C. r., **114** (1892), 226.

(19) Shimo and Asami, Published in the 6th meeting of the Chemical Research Institute of Non-Aqueous Solutions in 1954.

was dissolved but the hydroxide remained undissolved. By putting it at room temperature, crystals or a viscous liquid was produced as a reaction product. When crystals were produced, the upper clear solution was transferred into another pressure bottle through filter paper at the (b) part. The product was washed twice with 50 cc of distilled liquid ammonia and the remaining ammonia was removed under reduced pressure. The side tube was detached at the (a) part. The crystals were quickly taken out caring not contaminated with the remaining hydroxide and dried in a desiccator containing sulphuric acid for the sample.

After confirming that the sample was free from ammonia with a test paper wetted with phenolphthalein, it was used for the determination of the alkali metal and etherification.

One or two tenths gram of the reaction product was titrated with a decinormal hydrochloric acid using methyl orange as an indicator, the result being shown in Table 2.

Table 2

Kinds of alkali hydroxides	Mole ratio in the reaction	Mean percentages of the alkali metals in the reaction products	Mean mole ratio in the substitution metal/ <i>d</i> -mannitol
LiOH	1	7.78	2.1
		9.52	2.7
NaOH	1	8.52	2.4
		—	—
(C ₂ H ₅ OK	1	27.23	1.7)
KOH	1	19.79	1.1
		26.93 ^(a)	1.7
	1	16.39 ^(b)	0.9
vii)	1	17.81	1.0
		18.29	1.0
		18.93	1.1
		19.48	1.1
		20.47	1.2

The loss of weight of commercial lithium hydroxide used in the experiment by warming in vacuo was 2%. Purities of commercial sodium and potassium hydroxides were 93% and 85%, respectively.

(i) Five tenths and six tenths gram of the resulting crystal were obtained by using commercial wet sandy lithium hydroxide.

(ii) Four tenths gram of the produced crystal was obtained by using powdered lithium hydroxide obtained by warming and drying commercial product in vacuo.

(iii) Commercial sodium hydroxide granules gave no crystal though they were used by changing forms as in case of potassium hydroxide. The reaction product was unseparable viscous liquid.

(iv) Six tenths gram of metallic potassium was dissolved in 2.8 grams of absolute alcohol, mixed with 10 cc of liquid ammonia and reacted with 40 cc of liquid ammonia solution containing 3 grams of *d*-mannitol. The product was white powder weighing 2.6 grams.

(v) Reacting with commercial granular potassium hydroxide, 0.7 gram of crystal was obtained.

(vi) When 10 cc of liquid ammonia were added to 4 grams of an alcohol solution containing 0.9 gram of commercial granular potassium hydroxide, precipitate (A) was produced. By adding 40 cc of liquid ammonia solution containing 3 grams of *d*-mannitol to the above solution, 1.7 grams^(a) of white powdery precipitate was produced, while the former precipitate (A) disappeared. From the upper clear solution 0.5 gram^(b) of crystal was separated. When the first precipitate (A) was washed with liquid ammonia and reacted with a liquid ammonia solution of *d*-mannitol, the precipitate disappeared, but no reaction product was obtained.

(vii) When 10 cc of liquid ammonia were added to 1.4 grams of an aqueous solution of 0.9 gram of commercial granular potassium hydroxide, a precipitate (B) was produced. By adding 40 cc of liquid ammonia solution containing 3 grams of *d*-mannitol to the above solution, a minute amount of crystals was produced, but the precipitate (B) did not almost disappear. When the first precipitate (B) was washed with liquid ammonia and reacted with a liquid ammonia solution of *d*-mannitol, 2.4, 2.6, 3.4 and 3.8 grams of crystals were obtained from each reaction.

By mixing the equimolecular amount of lithium or potassium hydroxide with *d*-mannitol in liquid ammonia at room temperature, the reaction product separated out as colorless leaves or cubes consuming one part of the hydroxide. When sodium hydroxide was used as an alkali hydroxide, the product was unseparable viscous liquid but not crystal. In case of lithium hydroxide, the product was di-substitution product having weak hygroscopic property, while in case of potassium hydroxide strongly hygroscopic mono-substitution compound. In each reaction, the alkali hydroxide reacts very slowly, not consuming completely. It takes generally one day until crystal begin to separate out, though it is sometimes one hour.

3. Reaction between alkali metal compounds of *d*-mannitol and alkyl halides

(i) Reaction in liquid ammonia

In liquid ammonia, alkali mono- and di-substitution compounds of *d*-mannitol did not react with benzyl chloride or iodide at room temperature or at $-50\sim-60^\circ$. But liquid ammonia directly reacted with the two benzyl halides, producing benzylamine derivatives, which decomposed into *d*-mannitol.

(ii) Reaction in non-polar solvents

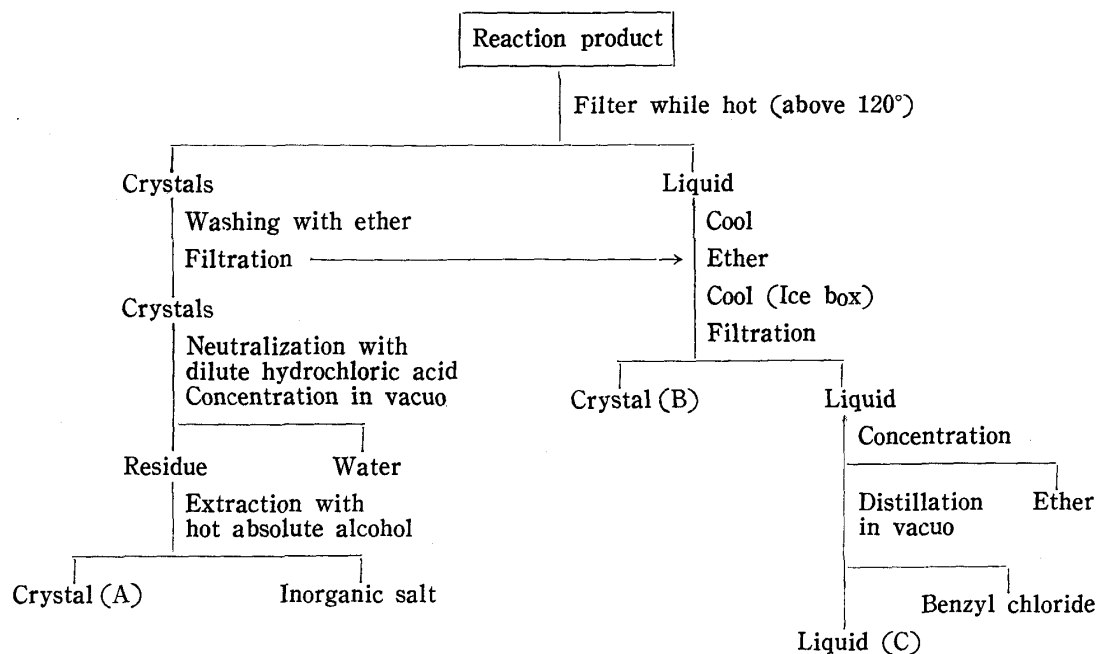
The alkali substitution compounds did not react with the two benzyl halides in dehydrated benzene nor xylene at their boiling points.

(iii) Direct reaction with benzyl halides

The alkali substitution compounds, except lithium compound, reacted directly with excess of the two kinds of benzyl halides at $130-180^\circ$ in the lapse of 1-2 hours, respectively, producing colorless thin crystals (almost square), m. p. $146-7^\circ$ in the yield less than 11%, and orange colored viscous solution. Except the case of lithium compound, the same reaction product was obtained, notwithstanding the difference of the kinds of the alkali metals, the alkali substitution compounds and benzyl halides.

An example of the separation of the reaction product was shown in the following diagram :

Table 3



(A) gave colorless needles, m.p. 163-4°, by recrystallizing from 95 percent alcohol, which was *d*-mannitol.

(B) gave colorless thin plate (almost square), m.p. 146-7°, by recrystallizing from 30 percent alcohol, which will be further examined.

(C) gave orange colored viscous liquid, which was not examined.

4. Minute examination of the crystal having the melting point of 146-7°

(i) When decomposed by heating, it gave no sweet odor. It burned with rather lustrous flame accompanied with a small amount of soot.

(ii) It contained no halogen nor nitrogen.

(iii) When 0.1 gram of the crystal was heated with 0.5 gram of concentrated hydroiodic acid ($d = 1.7$) for 5 minutes on a boiling water bath, it gave a pungent liquid having smell similar to that of benzyl iodide. The reaction product was cooled, washed with ether, concentrated in vacuo and washed with cold alcohol. The resulting white substance gave a minute amount of colorless needles by twice recrystallizing from 95 per cent alcohol. A mixture of the crystal and *d*-mannitol showed no lowering of melting point. So the first crystal was assumed to be an ether derivative of *d*-mannitol.

(iv) Determination of the molecular weight of the crystal by the Rast method using camphor.

Sample, 1.396 mgr Camphor (m.p. 176.5°), 13.311 mgr Lowering of the melting point, 11.5°. By the calculation, the result gave 364.7 as the molecular weight, which was almost twice of that of *d*-mannitol and suggested the presence of two benzyl radicals, that was almost coincidental with molecular weight of *d*-mannitol

di-benzyl ether, 362.

Elemental analysis gave the following result :

Sample, 3.690 mgr	CO ₂ , 8.902 mgr	H ₂ O, 2.390 mgr
	C, 65.83%	H, 7.25%
Theoretical values as C ₂₀ H ₂₆ O ₆	C, 66.27%	H, 7.18%

The result suggested that the crystal should be *d*-mannitol di-benzyl ether.

(v) As the hydrogen atom of the primary alcoholic hydroxyl radical is mostly replaceable among three kinds of alcoholic hydroxyl radicals, the bromine water method, generally applied to the oxidation of water soluble polyhydric alcohols, was applied to the crystal. Half a gram of saturated bromine water was directly mixed with 0.1 gram of the crystal and slightly warmed on a water bath. After more than 10 minutes, it was completely decolorized with sodium bisulphite and made strongly alkaline, into which Fehling's solution was added drop by drop and boiled. No orange red colored precipitate of cuprous oxide, which was generally produced by equally treating *d*-mannitol, was not perceived, which showed that the crystal had no reducing power. Namely, the crystal was not oxidized as α, α' -primary alcoholic radicals of *d*-mannitol were changed into ether forms.

The crystal was therefore assumed to be *d*-mannitol- α, α' -di-benzyl ether, which was formerly unknown.

The compound was recrystallisable from water, methanol, ethanol; benzene, acetone, chloroform and ethyl acetate. It was very soluble in glacial acetic acid and pyridine, difficultly soluble in ether, petroleum ether, ligroin, carbontetrachloride and carbon disulphide even at their boiling points. It was soluble in liquid ammonia.

Conclusion

(1) *d*-Mannitol reacts with the same mole of alkali metals in liquid ammonia at room temperature, producing powderly substance, which were proved to be di-substituted compounds of the alkali metals.

(2) *d*-Mannitol reacts with the same mole of alkali hydroxides in liquid ammonia at room temperature, gradually producing crystals, except sodium hydroxide, which were proved to be di-substituted compound of lithium and mono-substituted one of potassium.

(3) These metal substituted compounds of *d*-mannitol do not react with benzyl chloride nor iodide in liquid ammonia nor non-polar solvents. But they directly react with the two benzyl halides, except lithium compound, in the halides, producing crystalline compounds, their melting points are 146-7° in both cases.

(4) This new compound having the melting point of 146-7° was confirmed to be *d*-mannitol- α, α' -di-benzyl ether, which was formerly unknown.