

THE PREPARATION OF ISOSORBIDE DINITRATE

Adil A. Al-Hemiri, Amer Shimran and Salih Abdul Jabbar

Chemical Engineering Department - College of Engineering - University of Baghdad - Iraq

Abstract

The aim of this work is to study the optimum conditions for the preparation of isosorbide dinitrate (1, 4:3, 6 dianhydro D-glucitol 2, 5 dinitrate) from D-sorbitol. The process involves the following stages:

1. Dehydration of D-sorbitol by concentrated sulfuric acid to produce isosorbide, which is characterized by two major factors: The reaction time and the catalyst to feed ratio. It was found that the optimum conditions for the dehydration of D-sorbitol using concentrated sulfuric acid were: 167 minutes time of reaction and 2.88 % catalyst to feed ratio giving a yield 75.9 % isosorbide.
2. Nitrating of isosorbide by a mixture of concentrated nitric acid and concentrated sulfuric acid to produce isosorbide dinitrate, which is characterized by one factor, viz., nitration to feed ratio. It was found that the Optimum condition: 610 % nitration to feed ratio where the yield of isosorbide dinitrate 89.4 %.

Introduction

Isosorbide

Isosorbide is considered as a raw material for the preparation of isosorbide dinitrate^[1]. It is used for the manufacture of surfactant, emulsifiers, plasticizers, polyethers, polyesters and epoxy resins. It is also used as diuretic drug in treatment of hypertension.

The preparation of dianhydride of D-sorbitol was apparently first mentioned in 1927^[2]. The method involves treating D-sorbitol with various dehydrating agents. The obtained amorphous material reported to boil at 157 °C at 3 mm Hg pressure. No crystalline product was obtained and no proof of homogeneity offered.

The first reported synthesis of a crystalline dianhydro sorbitol was made by Harden^[2]. This dianhydrosorbitol was described as a crystalline substance melting at 30 °C and rotating at +46.5.

Montgomery and Wiggins^[3,4] prepared isosorbide and isoamidine by dehydration of D-sorbitol and manitol respectively using hydrochloric acid as a catalyst under reflux for 75-95 hours. The syrupy product from this treatment was fractionally distilled; pure dianhydro manitol distilled first at 136-140 °C at 10 mmHg, and was obtained as crystalline in 30 % of the theoretical yield. Dianhydro sorbitol at 160-165 °C at 10 mmHg, and was obtained as crystalline in 59% yield. A slightly better yield of the latter but a poorer yield of the former was obtained when the mixture of hexitols was heated with hydrochloric acid for 12 hours, followed by fractionation of the product, which was mainly dianhydro sorbitol, and treatment of the residues with acid for a further 72 hours.

In this method, crystalline dianhydro sorbitol was obtained as 62% and dianhydro manitol as 10%

of the theoretical yield. Hockett^[2] prepared isosorbide using a sample of pure D-sorbitol with concentrated sulfuric acid, which gives a yield of 82 % crude product (melts at 55.9-57.9 °C). Montgomery and Wiggins^[4] prepared isosorbide from D-sorbitol using different reaction times and different amounts of concentrated sulfuric acid. Isosorbide was prepared by the dehydration of D-sorbitol in the presence of concentrated sulfuric acid. They use aqueous solution of 70% sorbitol and concentrated sulfuric acid, and the mixture was boiled for five hours at 120-130 °C. The yield was 62 %^[5]. Isosorbide was also prepared from D-sorbitol using sulfuric acid in boiling benzene, toluene or xylene. The best yield at a ratio 1-1.5% concentrated sulfuric acid to D-sorbitol were not more than 72.1 %^[6].

The separation and purification of isosorbide involves neutralizing the acid by a strong base, followed by filtration and vacuum distillation. Hockett^[2] used a solution of barium carbonate for neutralization the concentrated sulfuric acid followed by evaporation of water at reduced pressure, the residue was distilled under pressure of 2 mmHg, and an oil bath temperature between 160-170 °C. Montgomery and Wiggins^[3] used aqueous alcohol to dissolve the syrupy residue then neutralized with sodium carbonate and filtered. The filtrate was evaporated to dryness, then distilled under vacuum of 10 mm Hg and a temperature of 160-165 °C. Water was used to dissolve the oil layer then treated with barium carbonate and whole mixture distilled under vacuum^[5].

Isosorbide Dinitrate

Isosorbide dinitrate is an ester of nitric acid^[7] -C-O-NO₂. It contains a nitroxy group. This is distinguished from nitrates (-C-O-NO), which is

esters of nitrous acid, and from nitro compound (-C-NO₂) in which the carbon and nitrogen are directly bonded. Isosorbide dinitrate is used as a long acting vasodilator agent in the treatment of hypertonia angina pectoris and other cardio vascular diseases [1].

A three common methods me used for the production of isosorbide dinitrate depending on the nitration agent, these are:

1. Mixture of concentrated nitric acid and concentrated sulfuric acid.
2. Concentrated nitric acid.
3. Mixture of nitric acid, acetic acid and acetic anhydride.

Kochergin and Tikova^[1] studied the preparation of isosorbide dinitrate using a mixture of concentrated nitric acid and concentrated sulfuric acid (40% to 60% respectively). They used a syrup of isosorbide containing water added drop wise to the nitrating agent during one hour. The yield of the method is 65% at temperatures between -5 to 5 °C. The preparation of isosorbide dinitrate using a mixture of concentrated nitric acid and concentrated sulfuric acid is 88% and 12% respectively and was also reported elsewhere [8]. The best yield they got at 746% nitration to feed ratio was 87.53%.

Kochergin and Tikova^[1] studied the preparation of isosorbide dinitrate using concentration nitric acid. The yield obtained was 83.3% at 787% nitration to feed ratio at a temperature of -5 to -2 °C. They also studied the preparation of isosorbide dinilrate using a mixture of acetic acid and acetic anhydride with nitric acid. They reached a yield of 83-85% using approximately 630% nitration to feed ratio at a temperature of 5 to 10 °C. Jackson and Hayward^[9] studied the preparation of isosorbide dinitrate using a mixture of acetic acid, acetic anhydride added to nitric acid at a temperature of -2 to 5 °C. the mixture was added drop wise with stirring. The yield was 85-90% at 1880% nitration to feed ratio.

Isosorbide dinitrate may be separated as crude, white precipitate by pouring the reaction mixture in cold water, filtered off mid washed with cold water for several times [7]. Ethanol [1] and water [10] are good solvents for recrystallization of isosorbide dinitrate.

Experimental Work

Dehydration Unit

Figure (1) shows a schematic diagram of the laboratory experimental unit used for the dehydration of sorbitol by means of sulfuric acid and the separation of isosorbide from the reaction mixture.

Filly grams of D-sorbitol was added to the reaction

flask and heated to 110-120 °C until melting. An amount of (0.5, 1.375, 3.5, 5.6 and 6.5 g) of the catalyst and concentrated sulfuric acid was also added. The mixture was then heated to a temperature between 130-150 °C with stirring at 300 RPM and under vacuum of 20-30 mm Hg. The reaction time varied from 1 to 5 hours. After each period of time, the heating of the reaction mixture was stopped and water was added followed by the addition of excess barium carbonate. The mixture was then filtered to obtain isosorbide solution under vacuum of 5-10 mmHg. The isosorbide collected in the receiver flask as crude yellow oily material. The crystallization of the crude isosorbide was carried out by dissolving it in ethyl acetate 1:1 W/W and heating to 70 °C with continuous stirring, then the solution was left to cool down to 0-5 °C and the crystals of isosorbide were collected by filtration. Identification was by U.V. spectroscopy.

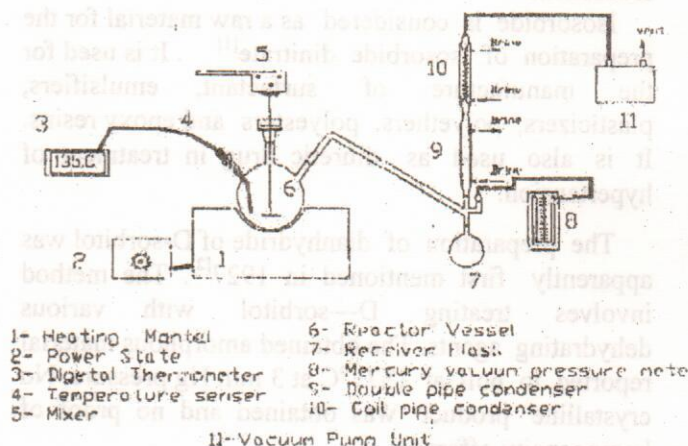


Figure (1) Dehydration Unit of Isosorbide

Nitration Unit

Figure (2) shows a schematic diagram of the laboratory experimental unit used for nitration of isosorbide to produce isosorbide dinitrate.

1.5 ml of water was added to isosorbide (5 g) in a reaction flask with stirring. The required amount of nitration mixture was then added (8.1-24.5 ml) drop wise during one hour and half, with cooling at 0-5 °C. Then the mixture was added to an amount of cold water with stirring. Isosorbide dinitrate precipitated as a white precipitate. Recrystallization was carried out by dissolving the crude isosorbide dinitrate in equal amount of ethyl alcohol with heating in water bath then the mixture was left to cool at -5 - 0 °C and the crystals of isosorbide dinitrate were collected by filtration. Identification was performed by HPLC.

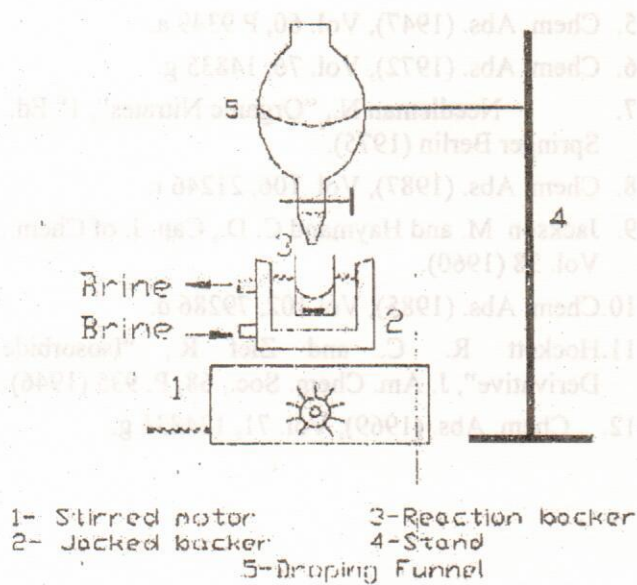


Figure (2) Nitration Unit

Results and Discussion

Preparation of Isosorbide by Dehydration of D-Sorbitol

Effect of Time of Reaction:

From Fig. (3) we can see that from 60 min. To 180 min., increasing the time of reaction results in an increase in the yield of the reaction. After approximately 180 min., there was a decrease in the yield for all catalyst ratios, because of the percent of concentrated sulfuric acid brought the pyrolysis of sorbitol and isosorbide [4,11].

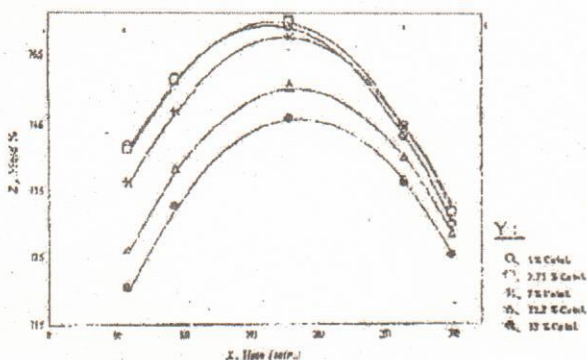


FIGURE (3) ISOSORBIDE Yield vs. Time at Constant Catalyst to Feed Ratio.

Effect of Catalyst Ratio:

From the same data mentioned above, a plot yield vs. catalyst ratio was constructed as shown in Fig.(4). From this figure we can see that for 1% to 4 % ratio the yield increases with increasing in catalyst to feed ratio. But beyond 4% approximately the increasing in catalyst ratio accomplishes the yield decreases. This

may be due to the fact that as the amount of sulfuric acid increases the pyrolysis of sorbitol increases and therefore the yield of isosorbide decreases [4,11,12].

Preparation of Isosorbide Dinitrate

The effect of nitrating ratio upon the yield of isosorbide produced by nitration of isosorbide is shown in Fig. (5). From this figure it is shown that at low nitrating ratio the yield of isosorbide dinitrate was extremely low. The figure also shows that the yield of isosorbide dinitrate increases were rapidly with increasing nitration to feed ratio up to approximately 650%. After this, further additions of nitrating mixture decrease the yield. The decreasing in yield is due to the nitrous acid, which is generally contained in nitric acid. In addition, nitrous acid may also be formed by reduction of nitric acid by isosorbide. In the presence of nitrous acid the isosorbide is violently oxidized, so the yield is diminished and explosion may occur [7].

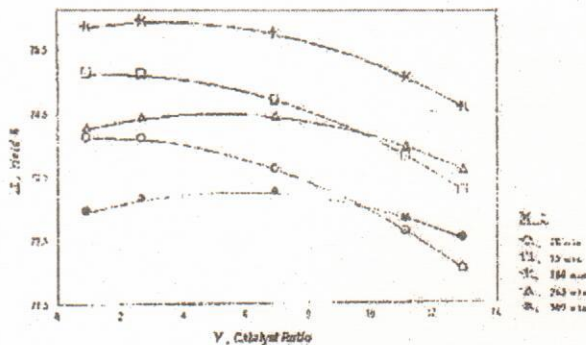


FIGURE (4) ISOSORBIDE YIELD vs. CATALYST TO FEED RATIO AT CONSTANT TIME

Conclusion

1. The optimum conditions for the preparation of isosorbide by dehydration of D-sorbitol using concentrated sulfuric acid at constant temperature (130-150 °C) and pressure (20-50 mmHg) is 2.88% catalyst to feed ratio and 167 minutes for reaction time, which gives maximum yield of 75.9 %.
2. Separation of isosorbide at concentrated sulfuric acid cause reducing in the yield of isosorbide.
3. The optimum conditions for die preparation of isosorbide dinitrate by nitration of isosorbide using a mixture of concentrated nitric acid and sulfuric acid (88 and 12% receptively) at constant temperature of 0-5 °C is 610% nitration to feed ratio which gives a maximum yield of 89.4%.
4. Nitration of isosorbide using concentrated nitric acid once (69-71%), nitric acid once again was unsuccessful for preparation of isosorbide dinitrate.

References

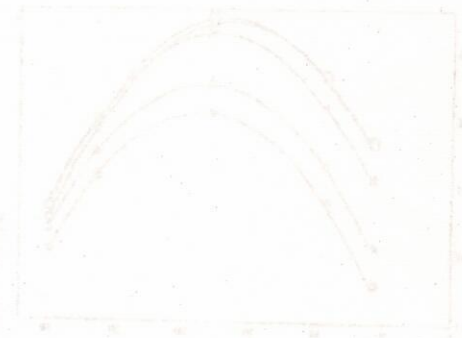
1. Kochergin P. and Titkova R., "Synthesis of Sorbide Dinitrate". Chem. Abs. (1960), Vol.54, 8647 h.
2. Hockett R. C., "The Structure of Isosorbide", J. Am. Chem. Soc., 68, P. 927 (1946).
3. Montgomery R. C. and Wiggins L. F., "Constitution of Dianhydrosorbitol", J. Chem. Soc., P. 390(1946).
4. Montgomery R. C. and Wiggins L. F., "Anhydrides of Polydric Alcohols", J. Chem. Soc., P. 437 (1947).

5. Chem. Abs. (1947), Vol. 60, P 9349 a.
6. Chem. Abs. (1972), Vol. 76, 14835 g.
7. Needleman N., "Organic Nitrates", 1st Ed., Springer Berlin (1975).
8. Chem. Abs. (1987), Vol. 106, 21246 r.
9. Jackson M. and Haymand C. D., Can. J. of Chem., Vol. 38 (1960).
10. Chem. Abs. (1985), Vol 102, 79286 d.
11. Hockett R. C. and Zief R., "Isosorbide Derivative", J. Am. Chem. Soc., 68, P. 935 (1946).
12. Chem. Abs. (1969), Vol. 71, 124831 g.



Effect of Time of Reaction

From Fig. (3) we can see that from 60 min. to 180 min., increasing the time of reaction results in an increase in the yield of the reaction. After approximately 180 min. there was a decrease in the yield for all catalyst ratios because of the pyrolysis of concentrated sulfuric acid brought the pyrolysis of sorbitol and isosorbide.



Effect of Catalyst Ratio

From the same data mentioned above, a plot yield vs. catalyst ratio was constructed as shown in Fig. (4). From this figure we can see that for 15% to 40% ratio the yield increases with increasing in catalyst to feed ratio. But beyond 40% approximately the increasing in catalyst ratio accomplishes the yield decreases. This

Conclusion

1. The optimum conditions for the preparation of isosorbide by dehydration of D-sorbitol using concentrated sulfuric acid at constant temperature (130-150 °C) and pressure (20-30 mmHg) is 3.88% catalyst to feed ratio and 107 minutes for reaction time which gives maximum yield of 72.9%.
2. Separation of isosorbide at concentrated sulfuric acid cause reducing in the yield of isosorbide.
3. The optimum conditions for the preparation of isosorbide dinitrate by nitration of isosorbide using a mixture of concentrated nitric acid and sulfuric acid (88 and 12% respectively) at constant temperature of 0-5 °C is 610% nitration to feed ratio which gives a maximum yield of 89.4%.
4. Nitration of isosorbide using concentrated nitric acid once (59-71%), nitric acid once again was unsuccessful for preparation of isosorbide dinitrate.