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SYNTHESIS OF SOME HEXANEDIOLS¹

E. VON RUDLOFF

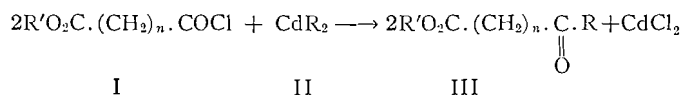
ABSTRACT

A general method for the preparation of 1,3-, 1,4-, and 1,5-hexanediols is described. The synthesis involves the preparation of a corresponding ketohexanoate, which is reduced to the diol with lithium aluminum hydride. Countercurrent distribution was found useful in the purification of small amounts of intermediates and end products. 1,2-, 1,6-, and 2,5-hexanediols were also prepared by known procedures. The infrared spectra of these diols have been recorded and their *p*-nitrobenzoates were prepared.

The analysis of mixtures of polyols obtained in the hydrogenolysis of methyl glucoside (1) required small amounts of various hexanediols for identification purposes. This paper describes a convenient method for preparing 3-, 4-, and 5-ketohexanoates, from which the 1,3-, 1,4-, and 1,5-hexanediols were obtained in 75–85% yield by lithium aluminum hydride reduction (2). It also describes the preparation of 1,2-, 1,6-, and 2,5-hexanediols by known procedures, and the preparation and characteristics of the *p*-nitrobenzoates. The infrared spectra of all of these hexanediols are recorded.

Hexanediols have been prepared by a variety of methods, none of which appeared to be generally applicable, and most suffered from the disadvantage that the starting materials were not readily available. Also, different types of crystalline derivatives were reported, making characterization by comparison difficult. No reference to the infrared spectra of these hexanediols could be found, although Kuhn (3) discusses the effect of hydrogen bonding on the infrared absorption band of the hydroxyl groups in 1,6-hexanediol.

The direct synthesis of hexanediols by general methods, such as the Grignard synthesis (4), did not appear feasible. A useful approach to their preparation appeared to be the synthesis of the corresponding keto- or hydroxy-acid (or ester), the latter being reduced readily to the hexanediol. When the synthesis of 4- and 5-ketohexanoic acids was attempted on a 10th molar scale by the methods of Winterfeld and Rönberg (5), Yoho and Levine (6), and Perlin and Purves (7) only very low yields of rather impure keto-acids were obtained. Purification by fractional distillation on this scale proved unsatisfactory. The method of Cason *et al.* (8) for the preparation of keto-esters (III) was then modified according to Perlin and Purves and satisfactory results were obtained when the difficulties of purification of 5 to 10 g. reaction products had been overcome. The synthesis involves the preparation of a given carboxy acyl chloride (I), via the semi-ester of the dicarboxylic acid, which was reacted with the appropriate dialkyl cadmium (II). The latter was prepared in isopropyl ether (7) from the Grignard intermediate.



Provided the semi-ester was pure, the keto-ester was obtained in a satisfactory state of purity on fractional distillation. When the semi-ester was isolated impure (e.g. monoethyl malonate), neither the ketohexanoate nor the hexanediol could be purified satisfactorily

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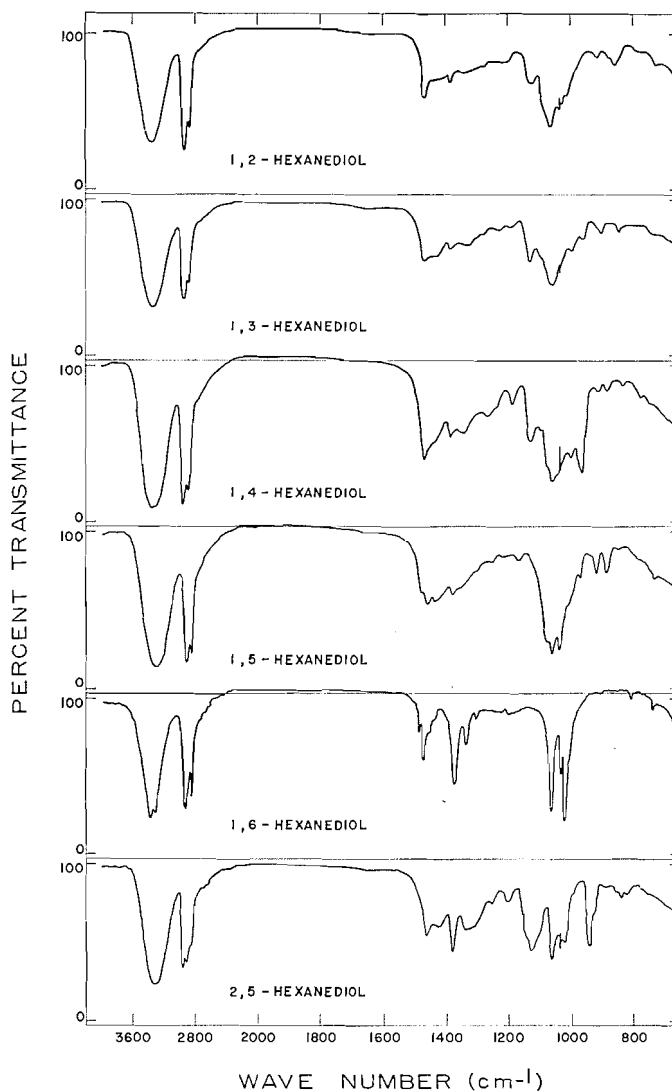


FIG. 1. Infrared spectra of hexanediols.

by fractional distillation. However, purification was possible by using countercurrent distribution. The distribution pattern of the keto-esters could not be obtained by weight analysis because of high solvent volatility. The impure keto-esters, therefore, were reduced and the reaction product was then fractionated and analyzed by countercurrent distribution, using weight analysis to obtain the distribution pattern. This analysis showed that the contaminant was the diol corresponding to the dicarboxylic acid component, indicating that the di-ester must have been present in the reaction mixture.

Reduction of the keto-esters with lithium aluminum hydride proceeded smoothly, and a good recovery of the products was obtained by salting out and extracting with ether containing 5-10% acetone. The use of methylal as solvent (9), as used in the reduction of adipic acid to 1,6-hexanediol, also gave satisfactory results. Catalytic reduction, as in the conversion of ethyl 5-ketohexanoate to 1,5-hexanediol in 85% yield by Hill and

Adkins (10), may sometimes be advantageous since the reaction can be carried out in ethanol or dioxane and larger quantities can be readily handled. The over-all yields of 1,5-, 1,4-, and 1,3-hexanediols were about 50%, 45%, and 30% respectively (based on the weight of semi-ester).

1,2-Hexanediol was prepared in about 45% over-all yield by α -bromination of caproic acid (11), hydrolysis to α -hydroxycaproic acid (12), and reduction with lithium aluminum hydride. Lithium aluminum hydride reduction of adipic acid (9) and acetyl acetone gave 1,6- and 2,5-hexanediol, respectively, in better than 80% yield. 2,5-Hexanediol was also prepared in about 95% yield by catalytic hydrogenation of acetyl acetone, using ethanol as solvent and copper chromium oxide as catalyst (10, 13).

Previously, it was found that hexanediols give a better yield of the *p*-nitrobenzoate than of the 3,5-dinitrobenzoate (1). Since the *p*-nitrobenzoates of hexanediols are crystalline compounds with high melting points, these were prepared as suitable derivatives. The 1,3-isomer was dimorphous, a phenomenon which was also observed with the *p*-nitrobenzoate of 1,3-propanediol.

The infrared spectra of the individual hexanediols (see Fig. 1), except those of 1,2- and 1,3-hexanediol, differ sufficiently from each other to allow identification. No significant differences were found in the spectra of the *p*-nitrobenzoates.

EXPERIMENTAL

All melting points are corrected and were measured with a Leitz heating stage microscope. The infrared spectra were recorded with a Perkin Elmer model 21 spectrometer equipped with a sodium chloride prism. Liquid compounds were mounted by the suspended film technique and solids by the potassium bromide disk technique (14). Counter-current distribution was carried out with a 100 tube modified E.C. Apparatus Co. fractionator having 40 ml. tube capacity (20 ml. upper and 20 ml. lower phase). *p*-Nitrobenzoates were prepared by the Schotten-Baumann reaction, using pyridine as base and solvent (15), and they were recrystallized from ethyl acetate - petrol and 2-butanone-petrol (b.p. 64°-66° C.).

Semi-esters of Dicarboxylic Acids

Succinic anhydride and glutaric anhydride were prepared by refluxing the dicarboxylic acids with excess acetic anhydride (16). The anhydrides were then converted to the monomethyl esters by the method of Ruggli and Maeder (17), e.g. succinic anhydride, 25 g. (0.25 mole), was refluxed with absolute methanol, 20 ml., for $\frac{1}{2}$ to 1 hour. The excess methanol was removed by evaporation in a rotary evaporator and the residue cooled to about 5° C., when it solidified. The crude material was recrystallized three times from ether to give monomethyl succinate, 29 g. (88% of theory), m.p. 58° C. Monomethyl glutarate was obtained similarly in about 80% yield and was purified by fractional distillation, b.p. 153°-155° C. at 10-11 mm.

Monoethyl malonate was prepared by saponification of the diethyl ester with the theoretical amount of potassium hydroxide (18). Diethyl malonate, 50 g. (0.31 mole), in 200 ml. absolute ethanol was added slowly to a solution of potassium hydroxide, 17.5 g. (0.31 mole), in 200 ml. absolute ethanol. The mixture was allowed to stand at room temperature until it was neutral. It was then heated and filtered hot. The potassium salt crystallized rapidly and after crystallization was complete it was filtered off, washed twice with cold ethanol and once with ether. The crystalline product was dissolved in a minimum of water and acidified in the cold with concentrated hydrochloric acid. On

standing, a little malonic acid crystallized, which was filtered off. The aqueous solution was then extracted repeatedly with ether. The ethereal extracts were washed once with water and then dried over anhydrous sodium sulphate. When the dried ethereal solution was reduced to a small volume, more malonic acid crystallized. The residue from evaporation of the filtered ethereal solution was fractionally distilled *in vacuo*, to give 29 g. monoethyl malonate (about 70% of theory), b.p. 131°–133° C. at 11–12 mm.

Synthesis of Ketohexanoates

The following is a typical example of the procedure adopted for the preparation of methyl or ethyl 3-, 4-, and 5-ketohexanoate.

To monomethyl succinate, 13.2 g. (0.10 mole), was added thionyl chloride (reagent grade), 15 g. (0.125 mole), and the mixture was left at room temperature under a reflux condenser equipped with a calcium chloride tube. After the evolution of gas had subsided, the solution was heated at 40°–45° C. for 3 to 6 hours and was left at room temperature for a further 16 hours. Excess thionyl chloride was then removed on a rotary evaporator at 15 mm. and 40°–45° C. (17). The residual acid chloride was dissolved without further purification in 25 ml. dry, peroxide-free isopropyl ether and added dropwise with stirring to a cooled mixture of the dialkyl cadmium. The latter mixture was prepared by reacting magnesium, 3.6 g. (0.15 g. atom), in isopropyl ether (7), 60–65 ml., with dry ethyl bromide, 17.4 g. (0.16 mole), in 25 ml. isopropyl ether in the normal Grignard manner, and adding to the cooled solution with vigorous stirring anhydrous cadmium chloride (dried in a vacuum oven at 70° C. for 18 to 24 hours), 14.7 g. (0.08 mole), in one portion.

After addition of the acid chloride was complete, the mixture was refluxed with stirring for 3 to 4 hours and was left at room temperature for 16 hours, and was then poured into excess ice and 10% sulphuric acid. The aqueous layer was separated and extracted three times with an equal volume of ether. The ethereal extracts were added to the isopropyl ether layer and the combined solution was washed once with 5% sodium bicarbonate solution, twice with water, and dried over anhydrous sodium sulphate. On evaporation of the ether a light brown liquid was obtained. It was distilled *in vacuo* and the fraction of b.p. 75°–78° C. at 11–12 mm. was collected. The yield of impure methyl 4-ketohexanoate was 9 g. (63% of theory).

Attempts to purify the keto-esters thus obtained by fractional distillation were unsuccessful, presumably because of the small amounts available. Countercurrent distribution, using 40 to 70% ethanol and petrol b.p. 64°–66° C. as solvent pair, gave a satisfactory separation, but about one-half of the keto-esters was lost on evaporation of the solvents. In this manner methyl 5-ketohexanoate, b.p. 100°–101° C. at 11–12 mm., was obtained in 20–25% over-all yield. Calc. for $C_7H_{12}O_3$: C, 58.31; H, 8.39%; saponification equivalent 144.17. Found: C, 58.17; H, 8.45%; saponification equivalent 145.

Reduction to Hexanediols

A solution of impure methyl 4-ketohexanoate, 4.3 g. (0.03 mole), in dry ether, 50 ml., was added dropwise with stirring to a suspension of lithium aluminum hydride, 1.9 g. (0.05 mole), in dry ether, 100 ml., which had been refluxed previously for $\frac{1}{2}$ to 1 hour. The usual precautions against moisture were taken. The mixture was refluxed for $\frac{1}{2}$ to 1 hour after addition of the ester, and, after cooling, ice water was added dropwise until excess lithium aluminum hydride had reacted. To the cold mixture was added cold 10% sulphuric acid, 10–20 ml., and after the mixture had cleared, it was saturated with potassium carbonate. The ether layer was withdrawn after adding 10 to 15 ml. acetone. The aqueous layer was then extracted exhaustively with ether containing 5–10% acetone. The ethereal

extracts were dried first over anhydrous potassium carbonate and then over anhydrous sodium sulphate. On evaporation of the ether, impure 1,4-hexanediol, 2.8 g. (80% of theory), was obtained. The mixture, 1.87 g., was fractionated by countercurrent distribution, using 2-butanone-water as solvent pair and 70 transfers. The distribution pattern was obtained by evaporating every second tube and weighing the residue in 20-ml. porcelain crucibles. Tubes 9-26 contained a viscous liquid, 0.45 g., which had an infrared spectrum identical to that of 1,4-butanediol. Calc. for $C_4H_{10}O_2$: C, 53.23; H, 11.49%. Found: C, 53.31, H, 11.19%. The *p*-nitrobenzoate, m.p. 175°-176° C., was undepressed in a mixture with an authentic specimen (m.p. 175°-176° C.). Tubes 28-40 contained 1,4-hexanediol, 1.25 g. The analytical data for this, as well as all the other hexanediols and their *p*-nitrobenzoates, are summarized in Table I.

TABLE I

	Hexanediols				<i>p</i> -Nitrobenzoates			
	B.p. at 0.3 mm. (air bath), ° C.	n_D^{20}	% C*	% H	M.p., ° C.	% C†	% H	% N
1,2- ¹	75-80	1.4431	61.11	11.75	101.5-102.5	57.79	4.87	6.63
1,3- ²	85-90	1.4455	60.91	11.84	78-79 and 93-95.5	57.50	4.88	6.71
1,4- ³	75-80	1.4515	60.93	11.97	124.8-125.4	57.55	4.82	6.72
1,5- ⁴	85-90	1.4490	60.94	12.10	103.5-104.2	57.63	4.72	6.62
1,6- ⁵	m.p. 41.0-41.8	—	61.23	12.10	121.8-122.5 ⁶	57.77	4.80	6.71
2,5- ⁷	80-85	1.4474	60.92	11.87	170.0-171.0	57.79	4.86	6.48

* Calculated for $C_6H_{14}O_2$: C, 60.98; H, 11.94%.

† Calculated for $C_{20}H_{20}N_2O_8$: C, 57.69; H, 4.84; N, 6.73%.

¹Levene and Haller (19): b.p. 110°-131° C. at 6 mm. (dinaphthylurethan m.p. 172°-174° C.).

²Glacet (20): b.p. 123°-123.4° C. at 13 mm., n_D^{20} 1.4461 (diphenylurethan m.p. 99.3° C.).

³Glacet (20): b.p. 127.5°-127.7° C. at 13 mm., $n_D^{16.3}$ 1.4530 (diphenylurethan m.p. 71° C.).

⁴Hill and Adkins (10): b.p. 89°-91° C. at 0.5 mm.

⁵Haworth and Perkin (21): b.p. 152° C. at 17 mm.; m.p. 42° C.

⁶Heyns and Woyrsch (22): m.p. 120° C.

⁷Duden and Lemme (23): b.p. 120°-122° C. at 12 mm.; n_D^{20} 1.4475.

In the same manner 1,5-hexanediol and 1,3-hexanediol were obtained in about 50% and 30% over-all yield respectively. In addition to 1,3-hexanediol, a considerable amount of 1,3-propanediol, *p*-nitrobenzoate, m.p. 109°-111° C. and 117°-118.5° C., mixed m.p. with an authentic specimen 111°-112° C. and 117°-118.5° C., was isolated.

Lithium aluminum hydride reduction of α -hydroxycaproic acid, adipic acid (9), and 2,5-hexanedione (acetonyl acetone) gave 1,2-, 1,6-, and 2,5-hexanediol respectively in 75-85% yield. α -Hydroxycaproic acid, m.p. 60°-62.5° C., was prepared in about 60% over-all yield by α -brominating caproic acid (11) and hydrolyzing the α -bromocaproic acid with aqueous potassium carbonate (12). Adipic acid, m.p. 151°-153° C., and 2,5-hexanediol, b.p. 192°-194° C., were obtained commercially. 2,5-Hexanediol was also prepared in better than 90% yield by hydrogenation over copper chromium oxide according to the method of Hill and Adkins (10).

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