SEPARATION OF EPIMERIC γ-ALDONOLACTONES IN THE SYNTHESIS OF RIBOFLAVIN

A. A. Shereshevskii and N. V. Gyach

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In the synthesis of riboflavin (vitamin B_2) the ability of D-arabonic acid or its salts to undergo epimeric conversion of the hydroxyl at C_2 with the formation of D-ribonic acid under specified conditions is used for the preparation of the latter. Similar reactions are reversible and in all cases lead to the formation of two epimers differing in configuration at C_2.

The epimeric conversion of the C_2 hydroxyl of aldonic acids is a particular case of carbohydrate reactions occurring under the action of bases and occasionally of acids. For monosaccharides these conversions have been studied fairly well [1]. A mechanism for this reaction has been proposed providing for the intermediate formation of the corresponding enol. Apart from epimerization at C_2 other conversions have been observed in the molecule including splitting off water, fission of a carbon–carbon bond, double bond migration (in the intermediate enol), etc. There have been attempts to use acids as catalysts in this reaction [2]. The epimer was obtained in very small yield after an extended time. The basis is a more effective catalyst, although the nature of the cation plays a definite role. Hydroxides of divalent metals are more effective than those of monovalent which is probably explained by stabilization of the enol as a result of interaction with divalent ions [3].

Several enzymes are known which catalyze epimerization reactions of monosaccharides such as glucoisomerase and arabinoisomerase catalyzing the epimeric conversion of glucose and arabinose [4].

Derivatives of monosaccharides and polyols undergo a similar conversion under conditions of catalytic hydrogenation over a nickel catalyst [5].

Epimerization of aldonic acids was effected for the first time in the presence of pyridine. On heating D-arabonic acid at 130°C for 3 h in the presence of pyridine a mixture of epimeric aldonic acids was obtained from which D-ribonic acid was isolated by fractional crystallization of the calcium and cadmium salts [6]. In more recent work [7] epimerization at 100°C (boiling) for 48 h was proposed to increase the yield of D-ribo-γ-lactone (I).

It was shown subsequently that salts of aldonic acids may be directly subjected to epimerization. On heating calcium D-arabonate in the presence of calcium hydroxide or pyridine 30-35% calcium D-ribonate was obtained [8, 9].

Separation of the resulting epimers was a separate complex problem.

Various methods of separating aldonic acids or their lactones have been described including fractional crystallization of calcium salts [8-10], barium salts [11], amides of the acids [12], lead or cadmium salts [13-16], separation through a brucine salt [17], through phenylhydrazides [18], or with the aid of ion-exchange chromatography [19]. Some investigations have been devoted to the isolation of pure (I) from a mixture of epimers. The preparation of (I) through iron ribonate has been proposed. Compounds releasing Fe^{2+} (reduced iron) have been used including hydrated iron oxide, iron oxalate, iron acetate, and other Fe^{2+} salts [20-23]. There are also studies in which (I) was isolated through zinc ribonate [24] and mercury ribonate [25].

The most efficient procedures for separating the epimeric lactones are methods which use the ability of (I) to form cyclic compounds with benzaldehyde and acetone as a consequence of the cis hydroxyls at C-2 and C-3 [26]. Arabonolactone forms such compounds with significantly more difficulty and under defined conditions does not form them.

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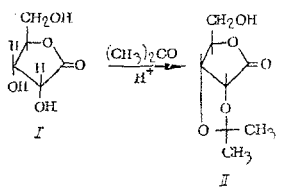
TABLE 1. Yield of (II) on Using Various Catalysts

Catalyst	Yield of (II)
Zinc chloride	46,2—51,0
Copper sulfate	48,5—53,0
Hydrochloric acid	56,3—65,4
Sulfuric acid	74,5—78,3
KU-2 Cation exchange resin in H^+ form	60,8—69,4

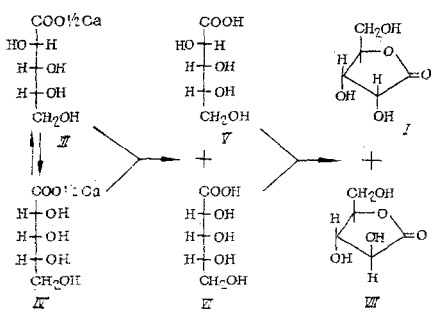
TABLE 2. Yield of (II) on Using Sulfuric Acid

Sulfuric acid, moles per mole (I)	Yield of (II), %
0,1	60,2
0,33	78,3
0,5	72,4
1,0	61,3
1,5	57,4

The process of separating (I) from a mixture of lactones through the product of reaction with acetone, viz. 2,3-isopropylidene-1,4-ribonolactone (II), has been studied in the present work.



The mixture of epimeric lactones was obtained as a result of an epimerization reaction of calcium D-arabonate (III) at 137°C in the presence of calcium hydroxide. From the obtained mixture of aldonic acid calcium salts the salt of D-arabonic acid, which is soluble with difficulty, separated. Compound (III) was not completely separated and after removal of calcium ions as the sulfate and lactonization a mixture of lactones was obtained containing 18-20% D-arabono-γ-lactone (VII) and 80-82% (I) (calculated on total epimers).



The content of epimeric lactones in the mixture was determined by GLC. Aldonolactones were chromatographed as trimethylsilyl derivatives [19, 27].

Reactions for obtaining (II) were carried out at room temperature in an excess of dry acetone in the presence of catalysts. Under these conditions (VII) underwent practically no interaction with acetone.

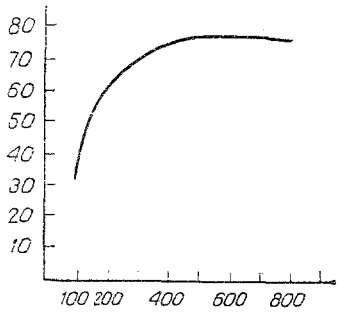


Fig. 1. Dependence of yield of (II) (%) on acetone excess (%).

On using anhydrous zinc chloride and copper sulfate as catalysts for the acetonylation reaction low yields of (II) were obtained. Mineral acids proved to have a stronger catalytic action (Table 1).

Cation exchange resin KU-2 in the H^+ form was used as catalyst for the acetonylation reaction of (I) for the first time.

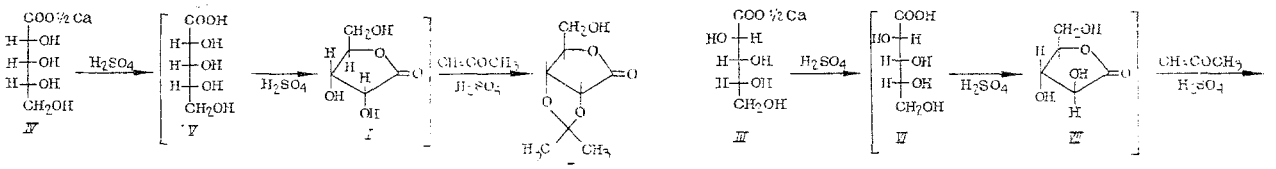
Reaction was carried out both under fixed conditions and by a continuous method using a glass column filled with cation-exchange resin. This method did not require neutralization of the acetone solution after reaction and was convenient for designing as a continuous process.

Best results were obtained using mineral acid. Use of sulfuric acid made it possible to obtain a yield of (II) of 78.3%, while only 0.3 mole sulfuric acid was required per mole lactone. On increasing the sulfuric acid loading the yield of (II) fell as a result of resinification of the reaction mixture (Table 2).

The excess of acetone used in the reaction proved to have an appreciable influence (Fig. 1). Maximum yield was obtained at a five-fold excess of acetone (volumes of acetone to mass of lactone). A further increase in acetone loading did not lead to growth of the yield.

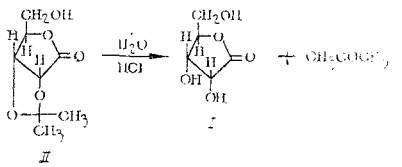
GLC using an internal standard was used to determine the duration of the process. It was shown that the reaction was complete in 1 h at 20°C.

A new scheme for obtaining (II) was developed using the calcium D-ribonate mixture (IV and III) directly as starting material. The dry mixture of salts was suspended in acetone in the presence of sulfuric acid. The reactions combined in one process by this were precipitation of calcium ions as sulfate with the formation of aldonic acid, lactonization under the action of sulfuric acid, and interaction of (I) with acetone with the formation of (II). Compound (VII) formed in the process did not react with acetone.



This method makes it possible to simplify the scheme for isolating (I); however, the yield of (II) was somewhat lower than on isolation from the mixture of lactones (56-60% calculated on IV).

To obtain (I), compound (II) was subjected to hydrolysis in acid medium. Several variants of the hydrolysis were considered including hydrolysis in the presence of sulfuric or hydrochloric acids, or KU-2 cation exchange resin in H^+ forms. Best results (90-95% yield) were obtained on carrying out hydrolysis in 15% hydrochloric acid at 60-80°C.



The obtained compound (I) contained no more than 1% (VII).

EXPERIMENTAL

Epimerization of (III). Water (165 ml), (III) (84 g), and hydrated calcium oxide (0.7 g) were loaded into an autoclave. The mass was heated to 133-137°C and stirred at this temperature for 5 h. The mass was then cooled to 78-80°C and filtered from solid. The filtrate was cooled to 0-5°C and crystallized at this temperature for 6 h. The precipitated unreacted (III) was filtered off and washed with water (5 ml) cooled to 0-5°C. Compound (III) (58.8 g) was obtained. Calcium ions were then precipitated from the mother liquor by pouring in concentrated sulfuric acid to pH 1.8. During the reaction the temperature must not rise above 90°C. At the end of precipitating calcium ions as calcium hydrogen sulfate active carbon was added to the reaction mixture which was heated to 85-90°C, stored at this temperature for 20 min, and filtered. The filtrate was evaporated to dryness in vacuum at 55-90°C. Technical lactone (11.96 g) was obtained containing 10.17 g total lactones (8.34 g I, 1.83 g VII), which corresponded to a yield of 62.7% of theory on the (III) which had reacted.

Preparation of (II). A. Technical lactone (20 g) containing (I) (14.4 g) was mixed with dry acetone (100 ml) in the presence of 94% sulfuric acid (1.5 ml). The mixture was stirred at room temperature for 1 h after which it was neutralized with 25% aqueous ammonia solution to pH 8.0. The precipitate of ammonium sulfate which formed was filtered out and the filtrate was evaporated to dryness at 40-50°C. A mixture was obtained consisting of (VII and II). The mixture was stirred with ice water (30 ml) for 5 min. Compound (VII) and other contaminants dissolved in the water. Compound (II), which is poorly soluble in water, was filtered off and dried at 50°C. Compound (II) (14.72 g: 78.3%) of mp 136-138°C was obtained.

B. The technical mixture of lactones (20 g) containing (I) (14.4 g) was mixed with dry acetone (100 ml) in the presence of dry KU-2 cation exchange resin in H^+ form (20 g). The mixture was stirred at room temperature for 3 h after which the cation exchange resin was filtered off. The filtrate was evaporated to dryness at 40-50°C. A mixture was obtained consisting of (VII) and (II). The mixture was stirred with ice water (20 ml) for 5 min. In this way (VII) dissolved in the water. Crystals of (II) were filtered off and dried at 50°C. Compound (II) (12.7 g: 69.5%) of mp 136-138°C was obtained.

C. The dry mixture of aldonic acid salts (10 g) containing (IV) (7.66 g) was stirred with dry acetone (50 ml) and 94% sulfuric acid (4 ml). Reaction was carried out at 50°C for 2 h and at room temperature for 3 h with continuous stirring. At the end of the reaction the mixture was filtered from the solid calcium sulfate which had precipitated during the reaction. The filtrate was then neutralized with aqueous ammonia solution to weakly alkaline reaction and then evaporated to dryness. The obtained solid containing (II) and (VII) was stirred with ice water (20 ml) for 5 min. Compound (VII) dissolved in the water. Crystals of (II) were filtered off and dried at 50°C. Compound (II) (3.08 g: 50.2%) of mp 136-138°C was obtained.

Preparation of (I). Compound (II) (14.72 g) was mixed with 15% hydrochloric acid (50 ml) and hydrolysis was carried out by stirring at 60°C for 1 h and at 80°C for 2 h. The reaction mixture was then evaporated to dryness and (I) (11.01 g: 95%) was obtained as a syrup which crystallized on standing to a colorless crystalline substance of mp 76-78°C.

Contamination by D-arabono-γ-lactone was 1%.

After crystallization from ethyl acetate white crystals were obtained of mp 78-80°C, $[\alpha]_D$ + 18.4 (5% in H_2O). Found, %: C 40.43; H 5.37. $C_5H_8O_5$. Calculated, %: C 40.54; H 5.44.

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STRUCTURE OF THE SIDE PRODUCT IN THE PREPARATION OF 4-METHYL-5-(β-HYDROXYETHYL)THIAZOLE

T. M. Filippova, A. R. Bekker,
T. I. Ozorova, V. M. Belova,
V. G. Mairanovskii, and
A. M. Yurkevich

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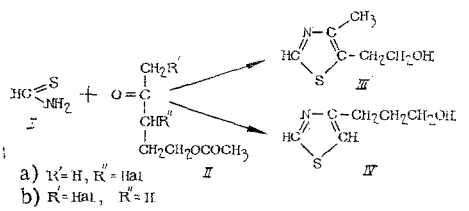
The intermediate product in the synthesis of vitamin B_1, 4-methyl-5-(β-hydroxyethyl)-thiazole (III) is obtained from thioformamide (I) and haloketone (IIa, b) [1]:



We can use either 3-bromo- (IIa), or 3-chloro-5-acetoxy-2-pentanone (IIb) as the haloketone. In the study of the synthesis of III from IIb, we found that in some cases GLC analysis of the reaction products showed that a side product is formed together with the desired product, with a much shorter retention time (Fig. 1). This compound has been preparatively isolated, and physicochemical methods have shown that its structure is 4-(γ-hydroxypropyl)-thiazole.

EXPERIMENTAL

The IR spectra were recorded on a UR-20 spectrometer (GDR) in a thin film. The PMR spectra were run on the "Hitachi R-20A" apparatus (Japan) with a 60 MHz working frequency

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