

[CONTRIBUTION FROM THE LABORATORY OF PHYSIOLOGICAL CHEMISTRY, LOYOLA UNIVERSITY SCHOOL OF MEDICINE]

## New Derivatives of *l*-Allonic and *l*-Altronic Acid. I<sup>1</sup>

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In a previous communication<sup>3</sup> from this Laboratory we announced the preparation of a crystalline lactone of *l*-allonic acid as well as the calcium salt of *l*-altronic acid and their conversion into crystalline *l*-allose and *l*-altrose, respectively. At that time lack of material prevented us from making a more detailed study of *l*-allonic and *l*-altronic acids and their derivatives. The present study was undertaken in order to determine in greater detail the physical constants of the two acids and their derivatives in general, and the rotational behavior of the *l*-allonolactone, previously reported, in particular.

The allonic and altronic acids used in this study were prepared from *l*-ribose by methods already published.<sup>3,4</sup> The *l*-allonic acid can be isolated in the form of the crystalline lactone previously reported, if the aqueous solution of the acid is evaporated and the resulting sirup heated on the steam-bath for several hours. This lactone has an initial specific rotation of  $+7.2^\circ$ , which becomes constant in twenty-four days at  $+3.6^\circ$ . The melting point of this compound is at  $129-130^\circ$ .

When, however, a freshly prepared aqueous solution of the free acid is concentrated rapidly under reduced pressure and the resulting sirup taken up in absolute ethanol without being exposed to a temperature higher than  $50^\circ$ , a crystalline substance is obtained having a composition corresponding to the formula  $C_6H_{10}O_6$ . It is therefore a lactone of *l*-allonic acid. In contradistinction to the previously reported lactone it shows an initial specific rotation of  $-54.8^\circ$ . A further distinction from the known lactone is its behavior toward dilute solutions of bases; for, whereas the former cannot be titrated in ice-water solution using phenolphthalein as indicator, the new lactone can be titrated practically quantitatively under these conditions. When freshly

dissolved in water both lactones are neutral to litmus. Rehorst<sup>5</sup> has found a similar differential instability toward dilute solutions of bases among the  $\delta$ - and  $\gamma$ -lactones that he studied.

Further evidence that this new lactone belongs to the  $\delta$ -series and that the lactone previously reported belongs to the  $\gamma$ -series is furnished by the rate of mutarotation of these two substances as shown in Fig. 1. The relatively rapid change in rotation of the new lactone as compared with the small and slow change of the previously reported lactone indicates that they belong to the  $\delta$ - and  $\gamma$ -series of lactones, respectively.<sup>6</sup> Obviously further direct evidence would be highly desirable before definitely ascribing a certain ring structure to these lactones, but the instability of the strongly mutarotating lactone would make direct methylation studies of doubtful value. Therefore until evidence to the contrary is brought forth we shall call the new, strongly mutarotating lactone the  $\delta$ -lactone of *l*-allonic acid and the previously reported lactone the  $\gamma$ -lactone of *l*-allonic acid.

The ease with which the ring can shift in the case of the  $\delta$ -lactone is shown by its peculiar behavior during the determination of its melting point. If a sample of this lactone is heated slowly (increasing the temperature about  $1^\circ$  per minute), it melts at  $129-130^\circ$ , that is, at the same temperature at which the  $\gamma$ -lactone melts. If, however, the temperature is raised more rapidly it will melt unsharply at  $140-144^\circ$ . An investigation revealed that slowly heating the  $\delta$ -lactone to its melting point ( $130^\circ$ ) was sufficient to change it into the  $\gamma$ -form. This observation explains why we were unable to observe a depression of the melting point of a mixture of the two lactones.

The mutarotation of free *l*-allonic acid is of interest in several respects. Its initial rotation of  $+11^\circ$  is less levo-rotatory than that of either of its lactones, hence it follows Hudson's lactone rule as modified for lactones of small rotation.<sup>7</sup> The allonolactones were considered to be the only

(1) Rehorst, *Ber.*, **63**, 2279 (1930).

(2) Haworth, "The Constitution of Sugars," E. Arnold & Co., London, 1929, pp. 23-24.

(3) Hudson, "Relation between Rotatory Power and Structure in the Sugar Group," Scientific Papers of the Bureau of Standards, No. 533, Government Printing Office, 1926, p. 288.

(1) These studies, a portion of which was reported on the program of the meeting of the American Chemical Society in Pittsburgh, Sept. 7, 1936, were in part abstracted from a dissertation submitted by Mr. McManus to the Graduate School of Loyola University in partial fulfillment of the requirements for the degree of Master of Science.

(2) Dr. W. C. Austin, whose untimely death occurred in November, 1935, participated in the initial phases of this problem.

(3) Austin and Humoller, *THIS JOURNAL*, **56**, 1153 (1934).

(4) Austin and Humoller, *ibid.*, **56**, 1152 (1934).

doubtful exception among the aldonic acid lactones cited, although Hudson already had predicted at that time that allonic acid would show a rotation in agreement with his theory. The peculiar type of mutarotation of *l*-allonic acid as shown in Fig. 1 strongly indicates that an aqueous solution of the acid changes upon standing in part into the  $\delta$ -lactone and this in turn changes into the more stable  $\gamma$ -lactone.

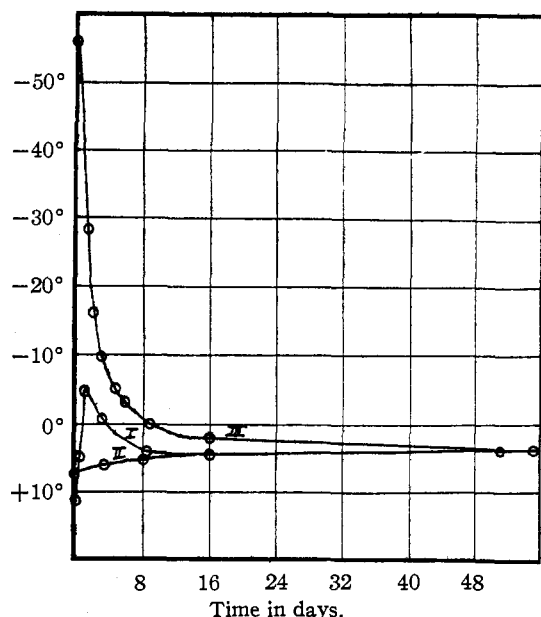


Fig. 1.—The mutarotation of *l*-allonic acid and its lactones: curve I, *l*-allonic acid; curve II,  $\gamma$ -*l*-allonolactone; curve III,  $\delta$ -*l*-allonolactone.

Attempts to prepare a crystalline lactone of *l*-altronic acid according to the method generally employed to prepare the stable form of lactones were not successful. However, when a freshly prepared aqueous solution of the acid is concentrated rapidly under reduced pressure without exposing the acid to elevated temperature a crystalline substance is obtained. An analysis of the substance for C and H indicates that this compound is not a lactone but the free *l*-altronic acid. This conclusion is confirmed by the finding that this substance is acid to congo red and can be titrated like any organic acid.

Recently Posternak<sup>8</sup> pointed out in a very brief announcement that the allomucic acid prepared by E. Fischer<sup>9</sup> by heating mucic acid in aqueous pyridine is actually a mixture of equal parts of *d*- and *l*-talomucic acid. Posternak did not report, however, the preparation of allomucic

acid. Therefore it was thought desirable to prepare allomucic acid from allonolactone and compare it with the substance obtained by the pyridine rearrangement of mucic acid. Allomucic acid prepared by the oxidation of *l*-allonolactone with nitric acid melts at 187.5° with decomposition and charring, and it crystallizes in rectangular prisms, whereas the substance prepared by Fischer's method from mucic acid melts at 166–171° with decomposition but no charring. A mixture of the two substances melts at 173°. Obviously both substances are optically inactive. The findings of Posternak together with our results seem to show that Fischer was mistaken in assuming that in the pyridine rearrangement of mucic acid both of the hydroxyl groups adjacent to the carbonyl groups are inverted. At present work is in progress to prepare derivatives of allomucic acid.

### Experimental

**Preparation of  $\delta$ -*l*-Allonolactone.**—A concentrated solution of the lactone in hot water was treated with a slight excess of sodium hydroxide. The solution was then chilled in ice water and an amount of sulfuric acid equivalent to that of the base was added. The solution was poured immediately into 10 volumes of absolute ethanol. After filtering off the precipitated sodium sulfate, the filtrate was concentrated rapidly under reduced pressure to a thin sirup. The sirup was taken up in four volumes of absolute ethanol and clarified. The filtrate was again concentrated under reduced pressure. During this second evaporation the lactone usually crystallizes out spontaneously. After crystallization was complete the crystals were filtered off and washed with alcohol and then with ether. The mother liquors yielded further crops on concentration. Recrystallization of the lactone from absolute ethanol did not change its physical constants. These together with analytical data are given in Table I.

**Conversion of the  $\delta$ -Lactone into the  $\gamma$ -Lactone.**—A sample of 0.2028 g. of the  $\delta$ -lactone having a specific rotation  $[\alpha]^{20-25}_D -46.9^\circ$  was heated slowly in a small flask to 130°. The lactone melted at this temperature. However, it failed to crystallize on cooling. The material was dissolved in water and the solution made up to 25 cc. After clarification to remove a slight amount of color, it was found that the solution now had a specific rotation of  $[\alpha]^{20-25}_D +3.7^\circ$ .

**Preparation of the Phenylhydrazide of *l*-Allonic Acid.**<sup>10</sup>—The phenylhydrazide of *l*-allonic acid was prepared from the  $\delta$ -lactone by the usual method. Its specific rotation and melting point are given in Table I. They are identical with those of a sample of the phenylhydrazide prepared from the  $\gamma$ -lactone. A mixture of the two did not show any depression of the melting point.

(10) The melting point of this compound given by Austin and Humoller<sup>3</sup> was an unfortunate error, and we take this opportunity to correct it here.

(8) Posternak, *Naturwissenschaften*, **23**, 287 (1935).

(9) Fischer, *Ber.*, **24**, 2136 (1891).

TABLE I  
ANALYSES AND PHYSICAL CONSTANTS OF NEW SUBSTANCES

Substance	M. p., °C.	[ $\alpha$ ] <sup>20-25</sup> <sub>D</sub> in water		Formula	Analyses, %			
		Init.	Final		Calcd.		Found	
					C	H	C	H
$\delta$ - <i>l</i> -Allonolactone	140-144	-54.8°	+3.66°	C <sub>6</sub> H <sub>10</sub> O <sub>6</sub>	40.4	5.7	40.9	5.9
<i>l</i> -Altronic acid	110	-8.1°		C <sub>6</sub> H <sub>12</sub> O <sub>7</sub>	36.7	6.2	37.3	6.5
Allomucic acid	187.5	Inactive		C <sub>6</sub> H <sub>10</sub> O <sub>8</sub>	34.3	4.8	34.2	5.1
<i>l</i> -Allonic acid phenylhydrazide	142-145	-23.6°						
<i>l</i> -Altronic acid phenylhydrazide	151-152	+18.4°						

**Preparation of *l*-Altronic Acid.**—A solution of 17 g. of calcium *l*-altronate in 400 cc. of hot water was treated with sufficient oxalic acid to remove the calcium quantitatively. The filtrate from the calcium oxalate was concentrated under reduced pressure to a thin sirup. The sirup was poured into ten volumes of absolute alcohol. A small amount of insoluble material was filtered off. Upon concentration under reduced pressure the filtrate yielded 10 g. of crystalline material by spontaneous crystallization. *l*-Altronic acid was recrystallized from absolute ethanol to constant melting point. The physical constants and the analysis are given in Table I.

**Preparation of the Phenylhydrazide of *l*-Altronic Acid.**—*l*-Altronic acid readily formed a phenylhydrazide when treated with phenylhydrazine in the usual manner. The substance was recrystallized from hot absolute ethanol to constant melting point of 151-152°. It has a tendency to separate out from a hot alcohol solution in jelly-like masses which upon standing assume crystalline form.

**Rearrangement of Mucic Acid in Aqueous Pyridine.**—The reaction was carried out in general according to the procedure of Fischer.<sup>9</sup> If the reaction mixture was allowed to come into contact with the metal of the pressure vessel during the heating period extensive destruction took place. If the reaction mixture was kept in a glass vessel during the heating, a yield of about 12% of a substance showing all the properties described by Fischer was obtained. This racemic talomucic acid was recrystallized from hot water for the melting point determination. It is interesting to note that racemic talomucic acid resembles allomucic acid much more in solubility than it does *d*- or *l*-talomucic acid.

**Preparation of Allomucic Acid.**—A solution of 1 g. of  $\gamma$ -*l*-allonolactone in 50 cc. of nitric acid of sp. gr. 1.15 was heated on the steam-bath. When the evolution of brown fumes of oxides of nitrogen became too vigorous, the reaction was controlled by removing the reaction mixture from the steam-bath and cooling. The solution was evaporated in this manner to about half its volume. It was then diluted to about 50 cc. and concentrated to a few cc. under reduced pressure. This process of diluting and concentrating was repeated once more. During the second concentration allomucic acid began to crystallize in the distilling flask. After crystallization had gone to completion, the crystals were filtered off and washed thoroughly with water. About 0.6 g. of allomucic acid was thus obtained. The acid was recrystallized by dissolving it in hot water,

concentrating the solution under reduced pressure and then cooling it for several days. The melting point and analysis of allomucic acid are given in Table I. Allomucic acid is quite insoluble in cold water but is much more soluble in hot water probably due to lactone formation, for after it has been thus dissolved it takes many days before it begins to crystallize again, even after concentrating the solution. For rotational studies 0.3461 g. of allomucic acid was dissolved in 10 cc. of a sodium hydroxide solution. No significant rotation could be observed.

All melting points cited in this paper are uncorrected for stem exposure. The authors wish to express their gratitude to Mr. D. Peterson of the Department of Biochemistry, The University of Chicago, for carrying out the micro carbon and hydrogen determinations cited in this paper.

### Summary

1. A new crystalline lactone of *l*-allonic acid has been prepared and some of its physical constants determined. From its behavior toward dilute alkali and from its rate of mutarotation it has been concluded that this substance is the  $\delta$ -lactone and that the previously prepared lactone is the  $\gamma$ -lactone of *l*-allonic acid.
2. Methods for converting one lactone into the other have been presented.
3. *l*-Altronic acid has been prepared and some of its physical constants recorded.
4. The phenylhydrazides of *l*-allonic and of *l*-altronic acids have been prepared and their melting point and specific rotation recorded. Their rotations show that these two substances follow the phenylhydrazide rule of rotation.<sup>7</sup>
5. Allomucic acid has been prepared. From a comparison of its properties with those of the substance obtained by the pyridine rearrangement of mucic acid it has been concluded that the two are not identical.

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