

1,3-CYCLOBUTANEDICARBOXYLIC ACID- A HISTORY OF MISTAKEN IDENTITY

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The synthesis of 1,3-cyclobutanedicarboxylic acid has been studied by many capable organic chemists. From 1881 to the present, a variety of synthetic methods have been reported. However, with one exception, all those published before 1950 are erroneous. Markownikoff and Krestownikoff (1, 2), Perkin (3), Perkin and Haworth (4), Simonsen (5), Perkin and Simonsen (6), and Guthzeit and Dressel (7) all suggested approaches to this synthesis but because of an interesting sequence of unusual reactions and incorrect assumptions, none produced the desired 1,3-diacid.

In 1881 Markownikoff and Krestownikoff reported the first supposed synthesis of the acid by self-condensation of ethyl- α -chloropropionate catalyzed by sodium ethoxide. Hydrolysis of the product produced an acid m.p. 170 C. Later Markownikoff (2) isomerized this acid to another acid, m.p. 138 C, which could be converted to an anhydride, m.p. 49-50 C. These were thought to be the 1,3-*trans*-acid, the 1,2-*cis*-acid, and the 1,2-*cis*-anhydride!

The peculiarity of the Markownikoff reaction, which required nucleophilic attack at an unactivated methyl group, attracted the attention of Ingold (8, 9). He repeated and confirmed Markownikoff's work. Moreover, he found that diethyl α -(chloromethyl)-glutarate and the corresponding bromo compound under the same conditions produced *trans*-1-methyl-1,2-cyclopropanedicarboxylic acid. If Ingold had converted his *trans*-acid to the *cis*-acid he could have shown that the Markownikoff acid and the product from the chloroglutarate were identical by mixture melting point comparisons.

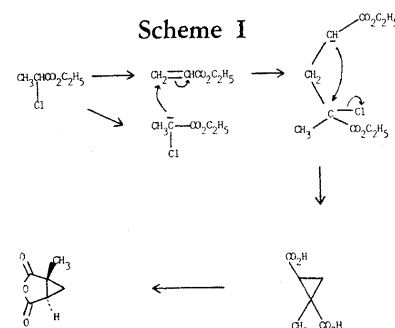
In 1950, Deutsch and Buchman (10) repeated Markownikoff's synthesis and showed that it produced the methylcyclopropanedicarboxylic acid described by Ingold (8, 9). This observation cleared up the vexing problem concerning the mechanism of the Markownikoff synthesis (Scheme I).

In 1898, Haworth and Perkin (4) showed that the acid with melting point 138 C produced by Markownikoff could be isolated from his original reaction mixture. They considered this acid to be the *cis*-1,3-diacid. Markownikoff had suggested that the acid of m.p. 138 C was *cis*-1,2-cyclobutanedicarboxylic acid. However, Perkin (3) had synthesized the authentic 1,2-diacid which also had melting point 138 C, but its anhydride melted at 78 C.

Haworth and Perkin (4) also investigated the reaction of formaldehyde with malonic ester, which produced a mixture of tetraethyl 1,1,3,3-propanetetracarboxylate, methylenemalonic ester, and a new tetraester which they assumed to be the 1,1,3,3-cyclobutanetetracarboxylate. Hydrolysis of this ester or the distillate produced when polymeric methylenemalonic ester was pyrolyzed gave a tetracarboxylic acid which could be decarboxylated to an acid of m.p. 129-133 C. This acid could be converted to an anhydride, m.p. 50-51 C. The similarity of melting points of this acid and its anhydride with those of the previous preparations convinced them that they had developed a new synthesis for the *cis*-1,3-diacid.

In 1908, Simonsen (5) published a variation of the Haworth-Perkin synthesis that involved boiling methoxymethylmalonic acid with 50% hydrochloric acid.

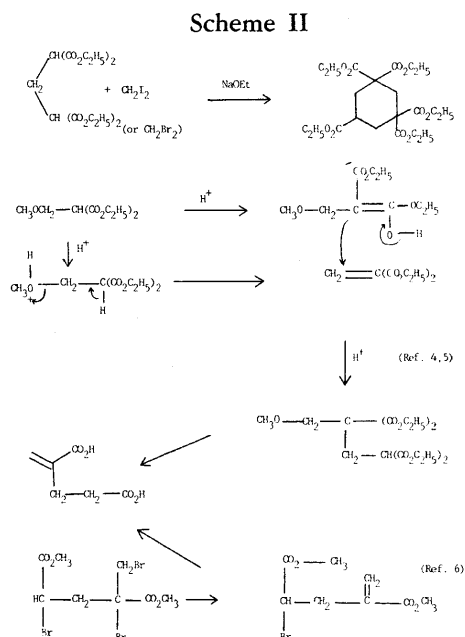
Perkin and Simonsen (6) treated dimethyl α, α' -dibromo- α -(bromomethyl)-glutarate with zinc in acetic acid and pro-



duced an acid with melting point of 131 C. Although they were aware that there were at least three ways the reaction could go, because of the melting point of the acid produced, they were certain that only the 1,3-cyclobutane diacid was produced. They pointed out that norpinic acid, 2,2-dimethylcyclobutane-1,3-dicarboxylic acid, (or a derivative) could add bromine and was unreactive to hydrobromic acid under conditions that 'opened' their acid. They attributed the difference in reactivity to the methyl group.

In 1942 Buchman (11) showed that Perkin's acid was really α -methylene-glutaric acid, Scheme II. Despite Buchman's work a paper appeared in 1952 (12) describing the reaction of $C_2H_5SCH_2Cl$ with sodiomalonic ester in ether. One of the products produced in low yield, an acid, m.p. 138 C, was identified as 1,3-cyclobutanedicarboxylic acid. The similarity of this reaction to Perkin's synthesis suggests this acid is also methyleneglutaric acid.

Guthzeit and Dressel (7) treated tetraethyl 1,1,3,3-propanetetracarboxylate with methylene iodide and sodium ethoxide and isolated a compound which gave fair analytical results for tetraethyl cyclobutanetetracarboxylate, and, after hydrolysis and decarboxylation, produced an acid m.p. 115 C. Analytical results for this compound did not correspond well to the cyclobutane diacid but the reaction has been suggested in some textbooks as a possible synthetic route to the 1,3-diacid.



Starting Material	Product	m.p. (C)	Ref.	Ionization Const.	Ref.	
$CH_3CHClCO_2C_2H_5$		<i>cis</i> -	143.0-143.5	11		
			138-139	2		
			135-136	4		
		<i>trans</i> -	170-171	1,4	pK_1 3.81	
		170	9	pK_2 5.28	19	
		anhydride	47.5-48	11		
			49-50	2		
			50-51	4		
$(CH_2)_2$ 		<i>cis</i> -	137-138	3	pK_1 4.16, pK_2 6.23	21
		<i>trans</i> -	130-131	3	pK_1 3.94, pK_2 5.55	21
		anhydride	76-78	3		
$CH_2=O$ and $CH_2(CO_2C_2H_5)_2$ or related method			131-132	4,11	pK_1 4.03	19
			130	8,9	pK_2 5.31	
			135-136	6		
		anhydride	51-51.5	11		
			50-51	4,6		
$CH_3CHCO_2C_2H_5$ $CH_2CHCO_2C_2H_5$ X		<i>cis</i> -	142	8		
		<i>trans</i> -	168	8,9		
		anhydride	liquid	8,9		
		X = Cl or Br				
$(HO_2C)_2$ 		<i>cis</i> -	131-132	16,17	pK_1 4.08, pK_2 5.12	21
			135-136	18		
		<i>trans</i> -	192-193	16,17	pK_1 4.11, pK_2 5.15	21
			190-191	18		
		anhydride	130-131	16,17		

TABLE I. Comparison of physical properties.

In 1958, Ebersson attempted to repeat this synthesis (13). He showed that the major distillable product was pentaethyl 1,1,3,3,5-cyclohexanepentacarboxylate. He found no evidence for cyclobutane ring formation.

There are several other reports of the failure of cyclobutane ring formation from substituted propanetetracarboxylates and methylene iodide (14, 15). Both of the 1,3-cyclobutanedicarboxylic acids have been prepared by Buchman (16, 17). His synthesis is outlined in Scheme III. The unusual melting point coincidences noted for the cyclopropane-, 1-2-cyclobutane-, and α -methylene-glutaric acids are also in evidence for the actual 1,3-diacids (Table 1). The very pure *cis*-acid (containing less than 0.5% of the *trans* isomer by gas chromatography of the methyl esters) melts at 135-136 C (18).

An early report on the ionization constants of *trans*- and *cis*-1,3-cyclobutanedicarboxylic acid gives those of *trans*-1-methyl-1,2-cyclopropanedicarboxylic acid and of α -methylene-glutaric acid respectively (19, 20). Values for the 1,3-cyclobutanedicarboxylic acids have recently been reported (Table 1). Bloomfield and Fuchs (21) observed only small differences between the ionization constants of the *cis*- and *trans*-1,3-cyclobutanedicarboxylic acids. Thus the pK values tell little about the conformation of the acids in solution.

X-ray crystallographic studies (22-24) have shown that the *trans*-1,3-acid is planar in the solid state. The *cis* isomer is bent (25, 26) while in an acid salt of the *trans* isomer $[C_4H_6(CO_2^-Na^+)_2 \cdot C_4H_6(CO_2H)_2]$ the acid is puckered and the dianion is planar. In solution the molecules are probably undergoing rapid ring inversions.

The main point to be learned from this brief history is that much confusion concerning chemistry and interpretation of the physical data would have been avoided if the most useful tool of the organic chemist (prior to the advent of modern instrumentation), the mixed melting point, had been fully utilized.

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