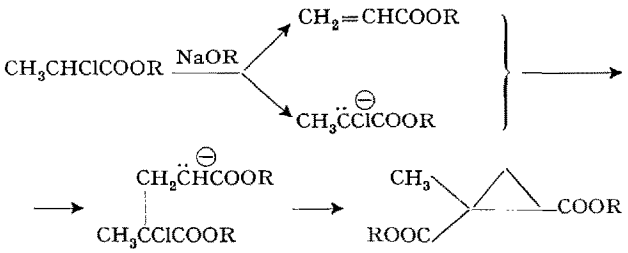
The Presumed Synthesis of 1,3-Cyclobutanedicarboxylic Acid by Markownikoff and Krestownikoff[1]

In a paper[2] published in 1881, MARKOWNIKOFF and KRESTOWNIKOFF reported that the diethyl ester of 1,3-cyclobutanedicarboxylic acid was formed in small yield by the action of dry sodium ethoxide on ethyl α-chloropropionate. Later studies[3] have apparently confirmed this result. Assuming it to be valid then, this synthesis is of interest: first, historically, as the first correctly interpreted alicyclic ring-synthesis[4]; secondly, since its mechanism[5] has never satisfactorily been explained; and, lastly, because it represents the only available preparative route[6] to the acid in question.

The present investigation discloses that the MARKOWNIKOFF-KRESTOWNIKOFF acid does not possess the assigned structure and is, in fact, identical with the well-known 1-methyl-1,2-cyclopropanedicarboxylic acid[7]. Certain of the reactions[8] of the supposed 1,3-cyclobutanedicarboxylic acid and of its derivatives are better in harmony with its formulation as a cyclopropane derivative; further the physical properties reported for the acid (both cis and trans forms) and for 1-methyl-1,2-cyclopropanedicarboxylic acid are in close agreement. The identity has been established by direct comparison of the acid of the Russian workers and of its derivatives with corresponding material prepared starting from methacrylic ester and diazoacetic ester[9].

The nature of the MARKOWNIKOFF-KRESTOWNIKOFF product having been clarified, the course of the reaction leading to its formation at once becomes apparent; it may be represented as follows[10]:



In support of the above mechanism may be cited the fact that application of the MARKOWNIKOFF-KRESTOWNIKOFF conditions to a mixture (1:1) of acrylic ester and α-chloropropionic ester resulted in a several-fold increase in yield of cyclic product. The same acid could also be obtained starting from a mixture of methacrylic ester and chloroacetic ester.

As a result of these findings[1], it follows: that the synthesis of 1,1-cyclobutanedicarboxylic ester by PERKIN (1883) was the first to be recorded of a four-carbon ring derivative; that authentic 1,3-cyclobutanedicarboxylic acid has not yet been prepared (studies relating to its synthesis are now in progress).

Note added in proof: Authentic 1,3-cyclobutanedicarboxylic acid has now been prepared by a straightforward synthesis[2]; the cis form was found to melt at 131–132°, the trans form at 189·8–190·3°.

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Zusammenfassung

Die Autoren stellen fest, daß die 1881 von MARKOWNIKOFF und KRESTOWNIKOFF synthetisierte Verbindung, die bisher als Cyclobutan-1,3-dicarbonsäure angesehen wurde, tatsächlich 1-Methylcyclopropan-1,2-dicarbonsäure ist.

[1] This investigation was carried out under a contract between the Office of Naval Research and the California Institute of Technology.

[2] W. MARKOWNIKOFF and A. KRESTOWNIKOFF, Ann. *208*, 333 (1881).

[3] W. MARKOWNIKOFF, Ber. *23R*, 432 (1890). – E. HAWORTH and W. H. PERKIN, jun., J. Chem. Soc. *73*, 330 (1898). During the last half-century, although the acid has been resynthesized in various connections (F. R. GOSS and C. K. INGOLD, J. Chem. Soc. *127*, 2776 (1925). – A. WASSERMANN, Helv. chim. acta *13*, 207 (1930). – E. R. BUCHMAN, A. O. REIMS, and M. J. SCHLATTER, J. Amer. Chem. Soc. *64*, 2703 (1942). – E. R. BUCHMAN *et al.*, unpublished) and the mechanism of its formation has been under discussion[5], the assigned structure has never been questioned.

[4] Cf. W. H. PERKIN, jun., J. Chem. Soc. 1347 (1929).

[5] W. MARKOWNIKOFF and A. KRESTOWNIKOFF, *loc. cit.* – C. K. INGOLD, J. Chem. Soc. *127*, 387 (1925). – F. R. GOSS and C. K. INGOLD, *loc. cit.* – Cf. W. H. PERKIN, jun., *loc cit.* – R. C. FUSON in GILMAN's *Organic Chemistry*, 2nd ed. (John Wiley and Sons, Inc., New York, 1943) Vol. I, p. 86.

[6] Cf. E. R. BUCHMAN, A. O. REIMS, and M. J. SCHLATTER, *loc. cit.*

[7] H. STAUDINGER, O. MUNTWYLER, L. RUZICKA, and S. SEIBT, Helv. chim. acta *7*, 401 (1924). – C. K. INGOLD, *loc. cit.* – F. R. GOSS and C. K. INGOLD, *loc. cit.* – K. v. AUWERS and E. CAUER, Ann. *470*, 284 (1929). – K. v. AUWERS and F. KÖNIG, Ann. *496*, 252 (1932). – K. E. WILZBACH, F. R. MAYO, and R. VAN METER, J. Amer. Chem. Soc. *70*, 4069 (1948).

[8] Notably the instability of the acid (cis form) toward hydrochloric acid (E. R. BUCHMAN, A. O. REIMS, and M. J. SCHLATTER, *loc. cit.*, p. 2704); cf. also the behavior of the diamine $C_4H_{10}N_2$ and of the dibromide $C_4H_6Br_2$ obtained from the acid by appropriate degradative techniques (E. R. BUCHMAN *et al.*, unpublished).

[9] The experimental details will be published elsewhere.

[10] Although the ring closure step involves a nucleophilic attack on a tertiary halogen grouping, the steric and other factors are such that the reaction may be expected to proceed smoothly (cf. K. E. WILZBACH, F. R. MAYO, and R. VAN METER, *loc. cit.*, p. 4071). The authors are indebted to Dr. SAUL WINSTEIN for a discussion on this point.

The Antibacterial Activity of Usnic Acid and Related Compounds

Since STOLL, BRACK and RENZ[1] reported the antibacterial activity of usnic acid, several publications[2] have appeared in which the original observations have been confirmed and extended.

In three of these papers[3] some attempts have been made to associate the activity of usnic acid with features of the molecular structure (I) as formulated by CURD and ROBERTSON[4]. In this connection, it may be of interest to record some observations on the antibacterial properties of a series of 1,3-diketo-2-acylindane derivatives having a similar triketone structure to that present in usnic acid.

[1] A. STOLL, A. BRACK, and J. RENZ, Exper. *3*, 115 (1947).

[2] A. MARSHAK, U.S. Public Health Reports *62*, 3 (1947). – A. MARSHAK, G. T. BARRY, and L. C. CRAIG, Science *106*, 394 (1947). – V. C. BARRY, L. O'ROURKE, and D. TWOMEY, Nature *160*, 800 (1947). – F. BUSTINZA and A. C. LOPEZ, Anales Jardín Bot. Madrid *7*, 1 (1948). – J. B. STARK, E. D. WALTER, and H. S. OWENS, J. Amer. Chem. Soc. *72*, 1819 (1950). – A. MARSHAK, W. B. SCHAEFER, and S. RAJAGOPALAN, Proc. Soc. Exper. Biol. Med. *70*, 565 (1949).

[3] V. C. BARRY, L. O'ROURKE, and D. TWOMEY, Nature *160*, 800 (1947). – F. BUSTINZA and A. C. LOPEZ, Anales Jardín Bot. Madrid *7*, 1 (1948). – A. MARSHAK, W. B. SCHAEFER, and S. RAJAGOPALAN, Proc. Soc. Exper. Biol. Med. *70*, 565 (1949).

[4] F. H. CURD and A. ROBERTSON, J. Chem. Soc. London 894 (1937).