[CONTRIBUTION FROM THE COLLEGE OF PHARMACY OF THE UNIVERSITY OF CALIFORNIA]

Methyl Tetronate, Methyl α-Chlorotetronate, Methyl α-Bromotetronate and Methyl α-Iodotetronate

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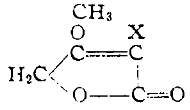
The tetronic acids are closely related structurally to ethyl acetoacetate and may be considered as derivatives of this compound. It is well known that when ethyl acetoacetate is treated with sodium and an alkyl halide the resulting substituted ethyl acetoacetate usually has the alkyl group attached to carbon. It was of interest to make some esters of the tetronic acids to see whether the alkyl group is attached to oxygen or to carbon. The first attempts at esterification of α-bromotetronic acid using dry hydrogen chloride and absolute alcohol failed,[1] and α-chlorotetronic acid resulted from the reaction. In a later experiment after passing hydrogen chloride through the solution for two weeks some evidence of esterification was obtained but the compound was not isolated in a pure state. Esterification by treating sodium α-bromotetronate with alkyl halides was not successful except in the case of *p*-nitrobenzyl bromide.[2] Diazomethane, however, reacted rapidly with all of the acids and the methyl esters that resulted could be isolated in a relatively pure state.

The carbon and hydrogen analysis in the case of methyl tetronate and the halogen analysis in the case of the other esters correspond to a lactone structure for the compounds and do not fit a hydroxycarboxylic acid ester structure. A methoxy estimation was carried out on the compounds to determine the position of the methyl group. If it is on the oxygen the percentage of methoxy found would be expected to be near the theoretical. If it is on the carbon the percentage found should be zero. The percentage of methoxy found shows that the compounds are oxygen esters.

	% Methoxy	
	Found	Calcd.
Methyl tetronate	25.6	27.2
Methyl α-chlorotetronate	19.6	20.9
Methyl α-bromotetronate	15.8	16.0
Methyl α-iodotetronate	12.6	12.9

The structure of these esters is then



where X is hydrogen, chlorine, bromine or iodine. This structure conforms to that found for the free acids and their salts.[2]

Experimental

The methoxy estimations were carried out using a semi-micro adaptation of the method of the British Pharmacopoeia, 1932. No empirical corrections were made for the incomplete precipitation of the alkyl iodide.[3]

The esters were prepared by suspending the corresponding acids in dry ether cooled to 0° and adding an excess of a solution of diazomethane in dry ether, also cooled to 0°. The excess diazomethane and ether was then evaporated on a steam-bath and the resulting ester crystallized from dioxane or methyl alcohol until a constant melting point was obtained.

Diazomethane was prepared from nitrosomethyl urea by Arndt's method.[4]

Methyl Tetronate.—M. p. 63°. *Anal.* Calcd. for $C_5H_6O_3$: H, 5.26; C, 52.6. Found: H, 4.96; C, 52.3.[5]

Methyl α-Chlorotetronate.—M. p. 66°. *Anal.* Calcd. for $C_5H_5O_3Cl$: Cl, 23.9. Found: Cl, 23.5.

Methyl α-Bromotetronate.—M. p. 116°. *Anal.* Calcd. for $C_5H_5O_3Br$: Br, 41.4. Found: Br, 41.1.

Methyl α-Iodotetronate.—M. p. 158°. *Anal.* Calcd. for $C_5H_5O_3I$: I, 52.9. Found: I, 52.6.

Summary

Methyl tetronate, methyl α-chlorotetronate, methyl α-bromotetronate and methyl α-iodotetronate have been made by the action of diazomethane on the corresponding acids. A methoxy estimation has been made on the compounds and this indicates that the methyl group is attached to oxygen and not to carbon. The structure of these esters is in accord with that previously found for the free acids and their salts.

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[1] Kumler, THIS JOURNAL, **60**, 857 (1938).

[2] Kumler, *ibid.*, **60**, 859 (1938).

[3] Niederl and Niederl, "Organic Quantitative Micro-Analysis," John Wiley and Sons, Inc., New York, N. Y., 1938, pp. 192, 198.

[4] *Org. Syntheses*, **15**, 3 (1935).

[5] The author is indebted to Professor P. L. Kirk's laboratory of the University of California Medical School for carrying out the micro-combustion on methyl tetronate.