NOTES

A New Synthesis of Methyl γ-Chloro-β-methylcrotonate and its Reformatsky Reaction

By Saburo Akiyoshi, Kenzo Okuno and Shizuo Nagahama

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Recently Hurd and Winberg[1] described the synthesis of ethyl γ-chloro-β-methylcrotonate from 3-chloro-2-methyl-1,2-epoxypropane in three steps. We have synthesized the corresponding methyl ester I by a simpler method, a modification of the Reformatsky reaction with compounds containing an active halogen atom.

Although the reaction between bromoacetone and methyl bromoacetate under the usual conditions with various solvents did not give the expected compound, chloroacetone and methyl bromoacetate in benzene–ether gave methyl γ-chloro-β-hydroxyisovalerate which was then dehydrated by phosphorus pentoxide to yield methyl γ-chloro-β-methylcrotonate (I).

The condensation of benzaldehyde with the methyl ester I was suggested by reports on the Reformatsky reaction of benzaldehyde with ethyl γ-iodo-β-methylcrotonate[1] and with α-chloro esters.[2] Of the various conditions tried, the reaction with Zn–$HgCl_2$ and toluene as the solvent gave the best results, yielding methyl β-styrylcrotonate in 25% yield, which was somewhat lower than that obtained from the bromo ester (57%),[3] or the iodo ester (34%).[1]

Experimental

Methyl γ-Chloro-β-hydroxyisovalerate.—The Reformatsky reaction of chloroacetone and methyl bromoacetate was carried out, as described in the literature,[4] in benzene, ether, and in mixtures of the two. A mixture of dry benzene (50 ml.) and dry ether (150 ml.) per 0.5 mole of reactants gave the best results. The yield was 32 g. (38.5%), b.p. 86.5–89° (6 mm.).

Methyl γ-Chloro-β-methylcrotonate (I).—By dehydration of 30.5 g. of the hydroxy ester by phosphorus pentoxide,[1] 16.5 g. (60.5%) of the crotonic ester I was obtained; b.p. 64–70° (6 mm.), d^{15}_{15} 1.1379; $n^{17}D$ 1.4626; *MR* 35.95, calcd. *MR* 35.86.

Anal. Calcd. for $C_6H_9ClO_2$: Cl, 23.86. Found: Cl, 24.41.

β-Styrylcrotonic Acid.—The condensation of the crotonic ester I with benzaldehyde was tried under the following conditions: magnesium with $HgCl_2$ in benzene–ether; magnesium with $HgBr_2$ in benzene–toluene; zinc with HgI_2 in benzene–toluene; and zinc with $HgCl_2$ in toluene. The last combination gave the best results.

In a clean dry three-necked flask equipped with a stirrer and a reflux condenser protected from the moisture, were placed 7 g. of zinc powder (which had been freshly treated with hydrochloric acid and dried with absolute alcohol and dry acetone) and 1.5 g. of $HgCl_2$. Then a solution of 8 g. of purified benzaldehyde and 11.5 g. of methyl γ-chloro-β-methylcrotonate (I) in 20 ml. of dry toluene was added and the mixture heated to boiling. The stirring and refluxing were continued for three hours; then the product was hydrolyzed and treated in the usual way. It was distilled at 4–5 mm. pressure to give an initial fraction (1 g.) boiling at 140–150° and a main fraction (3 g.) boiling at 181–183°, which was analyzed.

Anal. Calcd. for $C_{13}H_{14}O_2$: C, 77.20; H, 6.98. Found: C, 77.41; H, 6.28.

The ester was saponified with alcoholic potassium hydroxide solution. After the alcohol was removed, it was diluted with water, acidified and then extracted with ether. The ether was evaporated, and the acid residue recrystallized successively from benzene, dilute alcohol, and again from benzene to give white needles, melting at 156.8° (cor.). This material may correspond to "Form A" of styrylcrotonic acid reported by Fuson and Southwick.[3]

Institute of Applied Chemistry
Kyushu University
Fukuoka, Japan

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(2) R. E. Miller and F. F. Nord, *J. Org. Chem.*, **16**, 728 (1951).
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Pteroic Acid Analogs Containing Arsenic

By R. B. Angier, A. L. Gazzola, J. Semb, S. M. Gadekar and J. H. Williams

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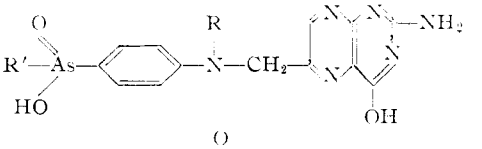
During the search for an improved oncolytic agent it was considered desirable to prepare a pteroic acid analog containing arsenic. This was particularly attractive because of the well known effect of some arsenic compounds on neoplastic tissue. During the past 150 years various inorganic and organic arsenic compounds have been tested as carcinolytic agents in animals[1] and a few of these compounds have shown some carcinostatic activity in the human. It was hoped that the pteridine nucleus might act as a carrier for the arsenic and thus increase its effectiveness.

A large number of derivatives and analogs of pteroic acid and pteroylglutanic acid have been synthesized since 1946. Among these there is only one example of a change in the acidic function of the *p*-aminobenzoic acid (PABA) portion of the molecule. This change involved the substitution of a sulfonic acid group for the carboxylic acid group of PABA.[2] Since *p*-aminobenzenearsonic acid (arsanilic acid) was readily available it seemed logical to use it to prepare a similar arsonic acid analog of pteroic acid. As a result of this idea seven pteroic acid analogs containing arsenic were synthesized using a modification of the procedure of Hultquist and Dreisbach.[3] Six of the com-



III, R = $-CH_2\overset{O}{\overset{\|}{C}}-NH_2$, R′ = –OH
IV, R = $-CH_2COOH$, R′ = –OH
V, R = H, R′ = $-CH_2COOH$
VI, R = H, R′ = –OH

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