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]

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(1) C. D. Hurd and H. E. Winberg, This Journal, **73**, 917 (1951).
(2) R. E. Miller and F. F. Nord, *J. Org. Chem.*, **16**, 728 (1951).
(3) R. C. Fuson and P. L. Southwick, This Journal, **66**, 679 (1944).
(4) C. R. Hauser and D. S. Breslow, *Org. Syntheses*, **21**, 51 (1940).

Pteroic Acid Analogs Containing Arsenic

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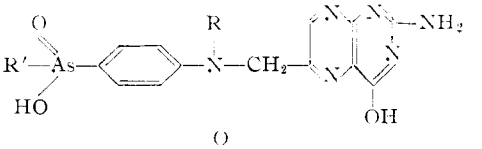
During the search for an improved oncolytic agent it was considered desirable to prepare a pteroic acid analog containing arsenic. This was particularly attractive because of the well known effect of some arsenic compounds on neoplastic tissue. During the past 150 years various inorganic and organic 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 = $-CH_2C(=O)-NH_2$, R′ = –OH
IV, R = $-CH_2COOH$, R′ = –OH
V, R = H, R′ = $-CH_2COOH$
VI, R = H, R′ = –OH

(1) C. M. Flory, *et al.*, *Cancer Research*, **3**, 729 (1943); J. Leiter, *et al.*, *J. Natl. Cancer Inst.*, **13**, 365 (1952); H. Dyer, "An Index of Tumor Chemotherapy," Federal Security Agency.
(2) M. Viscontini and J. Meier, *Helv. Chim. Acta*, **32**, 877 (1949).
(3) M. E. Hultquist and P. E. Dreisbach, U. S. Patent 2,443,165 (1948).

pounds are derivatives of *p*-aminobenzenearsonic acid and one compound is a derivative of *o*-aminobenzenearsonic acid.

Several of these compounds have shown moderate oncolytic activity against the glioblastoma 8110 in the mouse and against a mammary adenocarcinoma in the C3H mouse. Details of the work will be published elsewhere by S. L. Halliday and D. McKenzie of this Laboratory.

Experimental

General Procedure.—These compounds were all prepared by a modification of the procedure of Hultquist and Dreisbach.[3] The arsanilic acid derivative (0.5 to 0.67 mole) and 2,4,5-triamino-6-hydroxypyrimidine sulfate (I) (1.0 mole) were suspended in 2.5 l. of water and the mixture brought to *p*H 2.0. 1,1,3-Tribromoacetone (II) (1 mole) was then added. This was stirred vigorously and heated to 80° while keeping the mixture at *p*H 2 by adding 2.5 *N* sodium hydroxide solution. After heating at 80° for about 45 minutes the mixture was adjusted to *p*H 3.5, cooled to 15° and the product collected, washed with water and dried. The purification of this crude material varied depending upon the arsanilic acid derivative used in the synthesis.

4-(N-[(2-Amino-4-hydroxy-6-pteridyl)-methyl]-N-[carbamylmethyl]-amino)-benzenearsonic Acid (III).—Using the general procedure 146 g. of 4-(carbamylmethylamino)-benzenearsonic acid (Tryparsamide),[4] 318 g. of I and 354 g. of II gave 415 g. of crude product.

The bulk of this crude product (375 g.) was pulverized with a mortar and pestle and slurried in 24 l. of water containing 800 cc. of concentrated ammonium hydroxide (*p*H above 10). This was heated to 75° and stirred thoroughly for 30 minutes. Solid carbon dioxide was added to *p*H 8.0, the mixture was cooled to 20° and filtered with the aid of Celite. The filtrate was reheated to 75° and concentrated hydrochloric acid was added until a product precipitated and then redissolved (*p*H about 0.9). This solution was clarified with 10 g. of Norite and the filtrate while hot was treated with 10 *N* sodium hydroxide until a precipitate began to form (*p*H about 2.5). The solution was cooled to 20° and the product collected. This product was then redissolved in 400 cc. of concentrated hydrochloric acid and 4.5 l. of water added to obtain complete solution. After clarifying with 60 g. of Norite the filtrate was seeded and cooled to give a yellow crystalline product; yield 24 g.

For purposes of analysis a small portion of this compound was dissolved in a minimum amount of concentrated hydrochloric acid and then diluted with 120 volumes of water. The product was collected in a centrifuge, washed with water, acetone and ether and dried in a pistol at 130° for two hours.

Anal. Calcd. for $C_{15}H_{16}AsN_7O_5$: C, 40.1; H, 3.56; N, 21.8; As, 16.7. Found: C, 40.1; H, 3.98; N, 21.2; As, 16.2.

In 0.1 *N* sodium hydroxide III showed *E* (1%, 1 cm.) maxima of 945 at 260 mμ and 182 at 367.5 mμ; in 0.1 *N* hydrochloric acid the maxima were 605 at 267.5 mμ and 200 at 322.5 mμ.

4-(N-[(2-Amino-4-hydroxy-6-pteridyl)-methyl]-N-(carboxymethyl)-amino)-benzenearsonic Acid (IV).—Using the general procedure 110 g. of 4-(carboxymethylamino)-benzenearsonic acid, 240 g. of I and 266 g. of II gave a crude product which was collected as a damp cake and purified in the following manner.

The damp filter cake was slurried in 15 l. of a 0.1 *N* sodium hydroxide solution at 75–80° and heated at this temperature with good stirring for 30 minutes. The insoluble material was removed by filtration, the filtrate was reheated to 75° and treated with 135 cc. of a 30% calcium chloride solution. After stirring for 30 minutes this hot mixture (75°) was filtered and the lime cake was washed with 4 l. of hot water. The washings were added to the filtrate which was then adjusted to *p*H 2.5 with concentrated hydrochloric acid. The mixture was cooled and the solid collected and washed with water. The damp filter cake was dissolved in 3 l. of 0.15 *N* sodium hydroxide, a small amount of insoluble material was filtered off and the filtrate was clarified with 220 g. of Norite. The filtrate was adjusted to *p*H 1.5–2.0 with concentrated hydrochloric acid. A brown amorphous product appeared which after prolonged heating on the steam-bath changed to yellow needle-like crystals; yield 37 g.

A 0.2-g. sample was dissolved in dilute sodium hydroxide, clarified with Norite and acidified to *p*H 2. This was heated to effect solution and cooled again to obtain a crystalline product. This was collected, dissolved in 25 cc. of 2 *N* hydrochloric acid, diluted with an equal volume of water and cooled to obtain an analytical sample; dried in a pistol at 80° for one hour.

Anal. Calcd. for $C_{15}H_{15}AsN_6O_6$: C, 40.0; H, 3.33; N, 18.7; As, 16.7. Found: C, 39.6; H, 3.89; N, 18.5; As, 16.4.

In 0.1 *N* sodium hydroxide IV showed *E* (1%, 1 cm.) maxima of 858 at 260 mμ; and 184 at 367.5 mμ; in 0.1 *N* hydrochloric acid the maxima were 548 at 267.5 mμ and 194 at 322.5 mμ.

4-(N-[(2-Amino-4-hydroxy-6-pteridyl)-methyl]-amino)-phenyl-(carboxymethyl)-arsinic Acid (V).—Using the general procedure 150 g. of 4-aminophenyl-(carboxymethyl)-arsinic acid, 230 g. of I and 250 g. of II gave a crude product which was collected as a damp cake and purified in the following manner.

The damp filter cake was suspended in 16 l. of water at about 40° and dissolved by adding 200 cc. of a 10 *N* sodium hydroxide solution. After stirring for 30 minutes this was heated to 70°, treated with 370 cc. of 30% calcium chloride and filtered. Then at 50° the filtrate was treated with a 10% zinc chloride solution to *p*H 10.3 and filtered. The filtrate was acidified to *p*H 3.0, heated to 85° and acidified with hydrochloric acid until complete solution occurred. After seeding and cooling overnight the product was collected, washed with water, acetone and ether and dried; yield 31 g. Most of this product (29 g.) was dissolved in 400 cc. of 6 *N* hydrochloric acid, clarified with 5 g. of Norite and added to 1.2 l. of water at 65°. This was seeded and cooled overnight; yield 20.8 g.

For purposes of analysis a small sample of this material was given several more acid purifications as described above. The product was dried in a pistol at 130° for three hours.

Anal. Calcd. for $C_{15}H_{13}AsN_6O_4$: C, 43.3; H, 3.13; N, 20.2; As, 18.0. Found: C, 43.0; H, 3.93; N, 20.5; As, 17.8.

The compound appears to be the expected product minus one mole of water. The exact nature of this loss of water is not known. However, the ultraviolet absorption spectra and physical properties of V are similar to other members of this series all of which produced the expected and normal analytical results. Therefore, it seems probable that either lactam or anhydride formation has occurred involving the free carboxylic acid group and the nitrogen or arsenic atoms attached to the benzene ring.

In 0.1 *N* sodium hydroxide V showed *E* (1%, 1 cm.) maxima of 895 at 260 mμ and 192 at 365 mμ; in 0.1 *N* hydrochloric acid the maximum was 380 at 267.5 mμ.

4-(N-[(2-Amino-4-hydroxy-6-pteridyl)-methyl]-amino)-benzenearsonic Acid (VI).—Using the general procedure 65 g. of arsanilic acid, 120 g. of I and 125 g. of II gave 180 g. of crude product.

A portion of this material (70 g.) was dissolved in 4.5 l. of hot 0.1 *N* sodium hydroxide solution and purified as described for compound IV except that in the second acid precipitation the solid was dissolved by acidifying to give a 1 *N* solution; yield 8.9 g.

A portion of this product (1.0 g.) was dissolved in 100 cc. of hot 4 *N* hydrochloric acid, clarified with 1.0 g. of Norite and diluted with 100 cc. of hot water. After seeding and cooling the crystalline product was collected; yield 610 mg. Three hundred mg. of this material was dissolved in 300 cc. of a hot 0.2% sodium bicarbonate solution and a little insoluble material filtered off. The hot filtrate was treated with 100 cc. of warm 0.15 *N* hydrochloric acid solution bringing the solution to *p*H 1.5. The product crystallized immediately.

Anal. Calcd. for $C_{15}H_{13}AsN_6O_4$: C, 39.8; H, 3.32; N, 21.4. Found: C, 39.6; H, 3.63; N, 21.2.

In 0.1 *N* sodium hydroxide VI showed *E* (1%, 1 cm.)

(4) All of the arsanilic acid derivatives used as intermediates in this series are described in Raiziss and Gavron, "Organic Arsenical Compounds," The Chemical Catalog Company, Inc., New York, N. Y., 1923.

maxima of 950 at 257.5 mμ and 210 at 367.5 mμ; in 0.1 *N* hydrochloric acid the maxima were 605 at 267.5 mμ and 237 at 322.5 mμ.

4-(N-[2-Amino-4-hydroxy-6-pteridyl)-methyl]-amino)-3-bromobenzenearsonic Acid (VII).—Using the general procedure 115 g. of 3-bromoarsanilic acid, 200 g. of I and 225 g. of II gave 300 g. of crude product.

The crude product was dissolved in 18 l. of a 0.1 *N* sodium hydroxide solution at 75° and treated with calcium chloride and zinc chloride as described for compound V. The filtrate was adjusted to *p*H 2.0 and cooled; yield 22.0 g. The product was partially dissolved in 100 cc. of concentrated hydrochloric acid and then added to a liter of warm water. The material completely dissolved and quickly crystallized out again; yield 7.5 g.

A portion of this material (0.5 g.) was slurried in 10 cc. of 6 *N* hydrochloric acid. The compound dissolved and recrystallized immediately. The product was collected (0.3 g.) and redissolved in 10 cc. of water by adding several drops of ammonium hydroxide. This was mixed with an equal volume of concentrated hydrochloric acid, clarified with Norite and cooled to give a crystalline product.

Anal. Calcd. for $C_{13}H_{12}AsBrN_6O_4 \cdot HCl \cdot H_2O$: C, 29.7; H, 2.85; N, 16.0; Br, 15.2; Cl, 6.75; As, 14.3. Found: C, 29.6; H, 3.46; N, 15.9; Br, 15.0; Cl, 6.66; As, 15.0.

2-(N-[(2-Amino-4-hydroxy-6-pteridyl)-methyl]-amino)-benzenearsonic Acid (VIII).—Using the general procedure 104 g. of 2-aminobenzenearsonic acid, 230 g. of I and 250 g. of II gave 217 g. of crude product.

The crude product was suspended in one l. of water and dissolved by adding 10 *N* sodium hydroxide (about 250 cc.). This was clarified with Norite and then mixed with 1200 cc. of a 10 *N* sodium hydroxide solution. After cooling for two days at 5° the product was collected, redissolved in water (total volume 1100 cc.) and clarified with Norite. To this was added 1100 cc. of a 10 *N* sodium hydroxide solution and the solution was cooled overnight. The crystalline product was collected and recrystallized two more times in the same manner using 850 cc. of water, Norite and 850 cc. of 10 *N* sodium hydroxide each time. The crystalline sodium salt was then collected and added in portions to 100 cc. of cold concentrated hydrochloric acid. The sodium salt changed to the free acid and precipitated. This was diluted to one l. with water, cooled and the product collected, washed with water, acetone and ether and dried; yield 26.5 g.

For purposes of analysis a small sample was recrystallized twice as the sodium salt and then converted to the free acid.

Anal. Calcd. for $C_{13}H_{13}AsN_6O_4$: C, 39.8; H, 3.32; N, 21.4; As, 19.1. Found: C, 39.7; H, 3.81; N, 21.4; As, 19.7.

In 0.1 *N* sodium hydroxide VIII showed *E* (1%, 1 cm.) maxima of 805 at 255 mμ and 229 at 367.5 mμ; in 0.1 *N* hydrochloric acid the maxima were 492 at 247.5 mμ and 304 at 322.5 mμ.

4-(N-[(2,4-Diamino-6-pteridyl)-methyl]-amino)-benzenearsonic Acid (IX).—Using the general procedure 109 g. of arsanilic acid, 190 g. of 2,4,5,6-tetraaminopyrimidine sulfate and 218 g. of II gave 160 g. of crude product.

A portion of this product (58 g.) was dissolved in 11 l. of a 0.1 *N* sodium hydroxide solution at 70° and a small amount of insoluble black impurity was filtered off. The filtrate was warmed to 70°, treated with 100 cc. of a 30% calcium chloride solution and filtered. To the filtrate was added slowly enough of a 50% zinc chloride solution to bring the solution to *p*H 6.9. This was cooled and the product collected. This zinc salt was dissolved in approximately 1800 cc. of an 0.8 *N* hydrochloric acid solution at 80° and clarified with 50 g. of Norite. Upon cooling the filtrate the product crystallized; yield 1.85 g.

A portion of this material (400 mg.) was recrystallized from 100 cc. of 0.1 *N* hydrochloric acid; yield 200 mg. This was dissolved in 100 cc. of warm water containing 2 cc. of 1.0 *N* sodium bicarbonate solution, filtered and 40 cc. of a 0.1 *N* hydrochloric acid solution was added to the filtrate; yield of crystalline product 150 mg.

Anal. Calcd. for $C_{13}H_{14}AsN_7O_3$: C, 39.9; H, 3.58; N, 25.0. Found: C, 39.8; H, 4.24; N, 25.3.

In 0.1 *N* sodium hydroxide IX showed *E* (1%, 1 cm.) maxima of 990 at 257.5 mμ and 205 at 372.5 mμ; in 0.1 *N* hydrochloric acid the maxima were 680 at 267.5 mμ and 275 at 337.5 mμ.

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Nitration of the Tolyltriethylsilanes

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Recently[1] it was shown that copper nitrate can be used to nitrate phenyltrimethylsilane and that in this reaction the trimethylsilyl group functions as a very weak ortho–para director. It became of interest to determine whether the copper nitrate reagent could be used to nitrate substituted phenyltrialkylsilanes since in many of these compounds the tendency for cleavage of the trialkylsilyl group is more pronounced[2] than with the unsubstituted phenyl. The isomeric tolyltriethylsilanes were accordingly chosen for this study. It was hoped that in addition to the above information some conclusions might be reached concerning the directive effects of the triethylsilyl group compared to the methyl.

Nitration of *o*-tolyltriethylsilane resulted in a 50% yield of mononitrosilanes from which was identified 2-methyl-5-nitrotriethylsilane. The proof of structure of this isomer was accomplished by reduction to the amine, acetylation, and then cleavage of the triethylsilyl group with hydrogen chloride to yield *p*-acetotoluide. It seems likely that some 2-methyl-3-nitrotriethylsilane would also be formed in this reaction but we were unable to establish this definitely.

Nitration of *m*-tolyltriethylsilane resulted in a 74% yield of mononitrosilanes from which were identified 3-methyl-4-nitrophenyltriethylsilane and 2-nitro-5-methyltriethylsilane. The structure of the former was established by cleavage of the corresponding acetylated amine with iodine to form 5-iodo-2-acetaminotoluene. Treatment of the acetylated amine derived from 2-nitro-5-methyltriethylsilane yielded *p*-acetotoluide thus constituting a structure proof.

Nitration of *p*-tolyltriethylsilane gave a 60% yield of 4-methyl-3-nitrophenyltriethylsilane, since treatment of the corresponding amine with hydrogen chloride gave *o*-toluidine.

From the nitro isomers which were obtained it is quite apparent that the methyl group and *not* the triethylsilyl group is the dominating factor in determining the orientation. Thus in every case the incoming nitro group entered ortho or para to the *methyl* group even though in some instances this position was *meta* to the triethylsilyl while in others it was *ortho* or *para*. In addition the data tend to indicate (although admittedly the proof is on a less firm basis) the triethylsilyl group to be a weak ortho–para director like the trimethylsilyl. Thus the highest yield of nitrosilane isomers was

(1) R. A. Benkeser and P. E. Brumfield, THIS JOURNAL, **73**, 4770 (1951).

(2) R. A. Benkeser and H. R. Krysiak, *ibid.*, **75**, 4528 (1953).