

Displacement Reactions. XIII. Comments on the Article by Addelston and Goldsmith Entitled "Procedures for Detecting Errors in Chemical Literature" (1)

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An analysis of the critique by A. Addelston and U. J. Goldsmith has been made by citing quotations from several literature papers. It is concluded that errors of misunderstanding and misinterpretations can arise when such critiques are published without prior communication with the parties involved.

In March of 1966 a Symposium on Error Control in the Chemical Literature was held at the 151st National Meeting of the American Chemical Society. One of the published papers was by Aaron Addelston and Uriel J. Goldsmith (2).

One of the papers in our series "Displacement Reactions" (3) was considered in great detail. However, since it is our opinion that some misrepresentations were made, the present paper has been prepared.

The relevant quotations presented in Table I are reproduced from the original paper by Wagner and Davis (3). The statements appearing in the critique by Addelston and Goldsmith (2) have been reproduced from their article published eight months later.

Careful study of Table I shows that only reagent grade materials were used with the necessary precautions. Particular attention should be given to the following quotations:

"protected from atmospheric carbon dioxide. . ."
"concentration. . . was checked frequently with silver nitrate. . ."
"freshly distilled. . ."
"product was recrystallized from ether. . ."
"melting at 73.5–74.5°. . ."
"Analysis in the mass spectrometer. . ."
"The infrared spectrum of the cystine collected. . . is identical. . ."

These quotations from the paper by Wagner and Davis (3) describe the care with which the reagent grade chemicals were handled during the course of our work.

The claim that "this article gives elaborate mathematical treatment to presumably precise kinetic and isotope ratio data" (see Table I) is surprising since we used basic

statistical operations—namely, computation of a mean, a standard deviation, and a standard error of the mean—which are treated in standard undergraduate textbooks.

Another claim that "there are no analytical data for the synthetic products" can be questioned. Mass spectral and infrared analysis results were reported.

The "omission of preparative directions" for benzylthiolmethylphthalimidomalonate ester can be understood by noting that this compound has been prepared previously (without isotopic enrichment) by Wood and du Vigneaud, as referred to in Table I [reference 22 of the Wagner and Davis paper (3)]. The name of the compound is that used by the noted Noble prize winner, du Vigneaud, in describing his synthesis.

Since the word "sodium" occurred after the description of the addition of the reagents, the misinterpretation about the presence of a metal was made. Perhaps the directions were misleading. But sodium was mentioned. In our original paper (3), an equation was given with "Na" below the arrow (see Table I).

A portion of the letter of reply from the Editor of the *Journal of the American Chemical Society* to one of the authors of the Addelston and Goldsmith paper is reproduced as presented in their paper (2, 4):

"Thank you for your letter of January 20. We can only say that the manuscript was refereed by two thoroughly competent people who are in fact leaders in the general field of the mechanism of hydrolysis and aminolysis of esters. Apparently their examinations were primarily limited to matters of scientific content. . ."

We believe the problem is one of lack of communication by either letter or manuscript. It is evident that such lack of communication can only serve to compound misunderstandings and misinterpretations.

It is regrettable that there are some typographical errors in the paper by Wagner and Davis. These errors were

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Table I. Quotations from the Paper of Wagner and Davis (3) and Quotations of the Conclusions in the Paper by Addelston and Goldsmith (2)

Wagner and Davis (3) Jan. 1966	Addelston and Goldsmith (2) Aug. 1966
<p>A Experimental Section</p> <p>Potassium Hydroxide. Potassium hydroxide (Baker A. R.) was used to prepare stock solutions. The solutions were stored in polyethylene containers and were protected from atmospheric carbon dioxide by a drying tube containing Ascarite.</p> <p>Potassium Cyanide. Freshly opened potassium cyanide (Fisher A. R.) was used in the preparation of the cyanide solution. The cyanide solution was prepared directly in 0.040 M potassium hydroxide. The resulting solution was stored in a polyethylene container and was protected from atmospheric carbon dioxide by a drying tube containing Ascarite.</p> <p>Cystine. Reagent grade cystine,</p> <p>B KCN, $\frac{M \times}{10^{2b}}$ <p>Computed from the silver nitrate titration of the freshly prepared stock solutions.</p> <p>C Cystine solutions were prepared prior to each run by dissolving the necessary quantity of cystine (approximately 1.2 mg.) in 50 ml. of 0.0406 M potassium hydroxide and stored in a polyethylene container protected from atmospheric carbon dioxide by a tube containing Ascarite. The concentration of the cyanide solution was checked frequently with silver nitrate.</p> <p>D In the flask were placed 75.4 g. (0.315 mole) of freshly distilled ethyl bromomalonate, 58.2 g. (0.315 mole) of potassium phthalimide (Eastman Organic Chemicals), and 500 ml. of <i>m</i>-xylene (dried over CaCl₂). The resulting mixture was stirred and heated at 110–120° for 4 hr. It was refluxed for an additional 2 hr. at 140°. The mixture was allowed to remain at 4° for 12 hr. and then was filtered. The residue was extracted with cold benzene.</p> <p>E The washed residue was discarded and the filtrate and washings were combined and evaporated to dryness yielding a yellow oil. The yellow oil crystallized upon standing in an ice bath. The resulting crystals were washed with anhydrous ether until pure white. The product was recrystallized from ether by adding light petroleum ether (b. p. 60–70°). The yield of ethyl phthalimidomalonate melting at 73.5–74.5° was 41.9 g. (43.7% of the theoretical amount).</p> <p>F and air was bubbled through the solution for 9 hr. The resulting solution was tested with nitroprusside solution and gave a negative test for the sulfhydryl group. The solution then was neutralized to litmus and allowed to stand for 2 hr. The solution was evaporated <i>in vacuo</i> to half its original volume and the resulting precipitate was filtered, washed with water, and dissolved in hot hydrochloric acid. To the resulting solution was added a small quantity of decolorizing charcoal and after boiling a few minutes the solution was filtered. The product was precipitated from the clear solution with ammonium hydroxide. The resulting white crystals were filtered and washed with water and alcohol. The yield was 1.33 g.; this represented 44.6% of the theoretical amount. The infrared spectrum of the compound was identical with that of the <i>dl</i>-cystine (Nutritional Biochemicals). Analysis in the mass spectrometer indicated that the compound contained 1.31% N¹⁵.</p> </p>	<p>H but the starting materials were used without analysis or purification as received from commercial sources,</p>

Table I. Quotations from the Paper of Wagner and Davis (3) and Quotations of the Conclusions in the Paper by Addelston and Goldsmith (2) (Continued)

G mixture with glacial acetic acid to pH 5–6. The reaction mixture then was evaporated to one-fourth its original volume *in vacuo* after which the precipitated, unreacted cystine was separated by filtration. The product was washed first with water, followed by alcohol. The infrared spectrum of the cystine collected in this way is identical with that of the commercial sample (Nutritional Biochemicals). The resulting gas was handled and manipulated by means of a high-vacuum line. Since the gas evolved from the oxidation of ammonia is nitrogen, analysis by means of a mass spectrometer was the most accurate method of determining its isotopic composition.

I "Three separate experiments were performed for each of the 0, 50, and the 80% reaction samples. The reproducibility of the trails were very good. The measurements cited are on one sample of N₂ gas from each of the three experiments. In all, about 270 separate estimates were made on the isotopic ratios in these three separate experiments. ^aThis value is corrected for the background of N₂⁺ (28) at the time of the measurements. Typically it is between 12 and 30 mv. ^cThis value has been corrected for the *m/e* background at 29. Typically the correction is 0.400 to 1.000 mv. ^dAverage. ^eStandard deviation. ^fStandard error of the mean. ^gConfidence limits. ^hW. J. Youden, "Statistical Methods for Chemists," John Wiley and Sons, Inc., New York, N. Y., 1951, p. 82.

	Mean	37.18
	S.D.	0.09
	S.E.M.	0.03
	95% C.L.	37.18 ± 0.07
Isotope effect (randomization analysis) ^h		0.94%
	S.D.	0.26%
	S.E.M.	0.03%
	95% C.L.	0.94 ± 0.05%

L This article gives elaborate mathematical treatment to presumably precise kinetic and isotope ratio data,

K Table I. Kinetic Data on the Reaction of Cystine with Potassium Cyanide in Aqueous Solution

Cystine, M × 10 ^{4a}	KCN, M × 10 ^{2b}	pH ^c	Temp., ° C. ^d	k ₂ , M ⁻¹ sec. ^{-1e}
1.00	5.00	12.5	25	6.01 × 10 ⁻³
1.03	5.03	12.5	25	5.88 × 10 ⁻³
1.02	5.00	12.5	25	6.04 × 10 ⁻³
0.993	5.00	12.5	35	1.21 × 10 ⁻²
0.993	5.00	12.5	35	1.25 × 10 ⁻²
1.03	5.00	12.5	35	1.21 × 10 ⁻²

M HCl solution by the addition of NH₄OH. The yield of S-benzyl-*dl*-cystine melting at 215–216° was 1.62 g. (20.2% of the theoretical amount). Analysis of the product in the mass spectrometer indicated that the compound contained 5.14% N¹⁵.

N ammonium hydroxide. The resulting white crystals were filtered and washed with water and alcohol. The yield was 1.33 g.; this represented 44.6% of the theoretical amount. The infrared spectrum of the compound was identical with that of the *dl*-cystine (Nutritional Biochemicals). Analysis in the mass spectrometer indicated that the compound contained 1.31% N¹⁵.

O and there are no analytical data for the synthetic products.

(Continued on page 198)

Table I. Quotations from the Paper of Wagner and Davis (3) and Quotations of the Conclusions in the Paper by Addelston and Goldsmith (2) (Continued)

<p>P S-Benzyl-dl-cysteine.²² A 500-ml., three-necked flask was fitted with a stirrer, a thermometer, and a pressure-equalizing dropping funnel. In the flask were placed 160 ml. of a 1 : 1 mixture of 95% ethanol and water, 13 ml. of dioxane, and 16.8 g. (0.0381 mole) of benzylthiomethyl phthalimidomalononic ester. One drop of phenolphthalein was added, and the mixture was heated to 50°. NaOH (2 N, 38 ml.) was added dropwise with stirring at a rate to maintain the temperature at 55–60°. When all the alkali had been added, the temperature was allowed to fall spontaneously.</p> <p>(19) V. H. Bohme, H. Fischer, and R. Frank, <i>Ann.</i>, 563, 63 (1949). (20) H. R. V. Arnstein and P. T. Grant, <i>Biochem. J.</i>, 57, 360 (1954). (21) M. S. Dunn and B. W. Smart, <i>J. Biol. Chem.</i>, 89, 46 (1930). (22) J. L. Wood and V. du Vigneaud, <i>ibid.</i>, 130, 109 (1939); 131, 267 (193).</p>	<p>Q Omission of preparative directions for this compound (an obscure, and possibly new compound), where elaborate directions are given for every other compound used, many of which are well known.</p>
<p>R of S-benzyl-L-cysteine were mixed and added portionwise to the liquid as fast as the metal reacted. When all the mixture had been added and the solution remained a permanent blue in color for 15 min., ammonium chloride was added until the excess sodium was destroyed. The ammonia was allowed to evaporate spontaneously.</p> <p>T $\begin{array}{c} \text{COOH} \\ \\ \text{H}_2\text{NCH}-\text{CH}_2\text{SCH}_2\text{C}_6\text{H}_5 \end{array} \quad \begin{array}{c} \text{NH} \\ \\ \text{Na} \end{array} \left[\begin{array}{c} \text{COO} \\ \\ \text{H}_2\text{NCH}-\text{CH}_2- \end{array} \right] \text{air}$</p>	<p>S Directions to add a reactant portionwise to the liquid "as fast as the <i>metal</i> reacted" in a procedure where no metal is mentioned.</p>

A. Taken from the paper of Wagner and Davis (3). See page 10, second column, starting with line 31. B. Taken from (3). See page 8, first column, Table I and the footnotes to this table. C. Taken from (3). See page 12, first column, line 1. D. Taken from (3). See page 11, first column, line 23. E. Taken from (3). See page 11, first column, line 30. F. Taken from (3). See page 11, second column, line 52. G. Taken from (3). See page 12, second column, line 25. H. Taken from the paper of Addelston and Goldsmith (2). See page 127, second column, line 4. I. Taken from (3). See page 9, footnote to Table III. J. Taken from (3). See page 9, bottom of the text of Table III. "Mean" refers to the average of the measurements. "S.D." is the standard deviation. "S.E.M." refers to the standard error of the mean. "95% C.L." is the 95% confidence limits. These terms are defined in (3) and a footnote given to the book in which the manner of calculation is outlined. K. Taken from (3). See page 8, first column, top of Table I. L. Taken from (2). See page 127, second column, line 2. M. Taken from (3). See page 11, second column, line 16. N. Taken from (3). See page 11, second column, 20 lines up from the bottom. O. Taken from (2). See page 127, second column, line 6. P. Taken from (3). See page 11, first column, 14 lines up from the bottom. Q. Taken from (2). See page 127, second column, line 16. R. Taken from (3). See page 11, second column, line 43. S. Taken from (2). See page 127, second column, line 24. The word "metal" has been set in italics by Addelston and Goldsmith. The word did not appear in italics in our paper. T. Taken from (3). See page 9, Chart I.

corrected in a letter to the *Journal of the American Chemical Society* sent February 17, 1966. The corrections will appear in the Errata of the *Journal* in the December issue. It is interesting to note that all the citations quoted in Table I are from the **Experimental Section** and involve tiny type. It may be concluded that small type represents a hazard to both author and reader.

In conclusion, we feel that this rebuttal and the original accusations could have been avoided by direct communication between investigators.

LITERATURE CITED

- (1) Davis, R. E., Paper XII, *Tetrahedron Letters*, **1966**, 5021.
- (2) Addelston, A., and Goldsmith, U. J., *J. Chem. Doc.* **6**, 126 (1966).
- (3) Wagner, E. S., and Davis, R. E., *J. Am. Chem. Soc.* **88**, 7 (1966).
- (4) Personal communication from the Editor of the *J. Am. Chem. Soc.* soon after January 20, 1966, to A. Addelston and U. J. Goldsmith. The full text of the letter is quoted in (2).