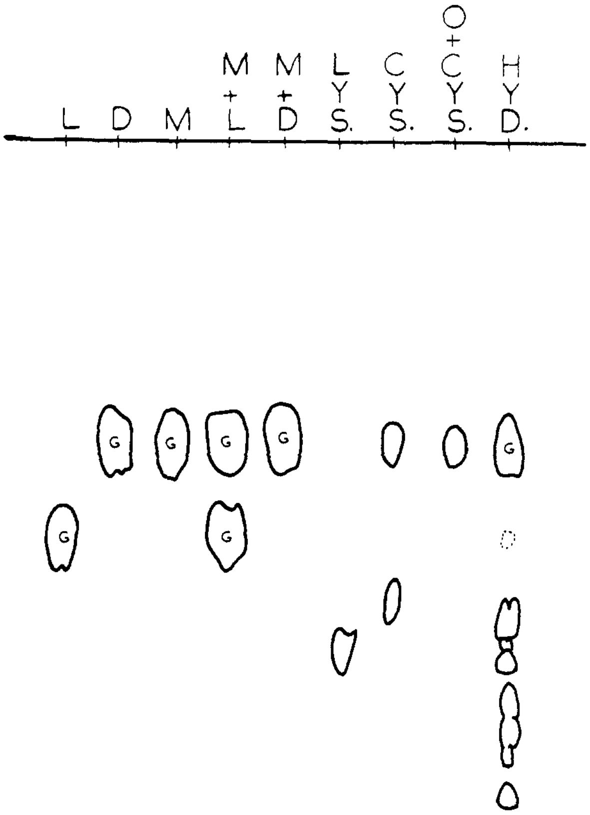

Fig. 3.—Descending chromatogram in methanol (80)–water (17.5)–10 N HCl (2.5)–pyridine (10). Abbreviations are as follows: Lys = L-lysine, cys = cystine, O + cys = H_2O_2 + cystine, hyd. = acid hydrolysate of *Mycobacterium tuberculosis* equiv. to 2 mg. dry wt. of organism, L, M, D as in Fig. 2, G = green ninhydrin color.

are all basic. The effect is evidently specific to DAP since a number of other synthetic amino acids, including the DAP homologs α,δ-diaminoadipic acid and α,ζ-diaminosuberic acid, could not be resolved into separate components on the methanol–water–pyridine chromatograms (*cf.* Table III). This suggests that the cationic forms of DAP are selectively and differentially absorbed by some asymmetric element in the paper, resulting in a different partition of the LL-isomer in certain solvents. Kotake[10] reported that DL-glutamic acid could be resolved in a solvent system containing the optically active *l*-methyl-(β-phenylisopropyl)-amine. To our knowledge, however, the resolution of stereoisomers of an aliphatic amino acid without the use of optically active solvents is a new observation. Certain aromatic amino acids have been resolved in this way.[11]

TABLE III

THE CHROMATOGRAPHIC BEHAVIOR OF A SERIES OF SYNTHETIC ALIPHATIC AMINO ACIDS IN A METHANOL (80)–WATER (20)–PYRIDINE (4) SYSTEM

Amino acid	R_f
α,δ-Diaminoadipic acid	0.23
α,ζ-Diaminosuberic acid[a]	.31
α-Aminopimelic acid	.65
ε-C-Methyllysine[b]	.33
α,γ-Diaminoheptanoic acid[c] (streaked)	.55
α,γ-Diamino-β-methylbutyric acid[c]	.35
α-Methylglutamic acid	.62
α-Amino-β-methylpimelic acid	.62

[a] Kindly supplied by Dr. D. Simmonds, Medical Research Institute, London. [b] Kindly supplied by Dr. A. D. McLaren, University of California. [c] Kindly supplied by Dr. H. E. Carter, University of Illinois.

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(10) M. Kotake, T. Sakan, N. Nakamura and S. Senole, THIS JOURNAL, **73**, 2973 (1951).

(11) C. E. Dalgliesh, *J. Chem. Soc.*, 3940 (1952).

THE RESEARCH LABORATORIES
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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, BOSTON UNIVERSITY]

A New Synthesis of Phloionic Acid[1]

BY WALTER J. GENSLER AND HERBERT N. SCHLEIN

RECEIVED MARCH 10, 1955

A synthesis of 9,10-dihydroxyoctadecanedioic acid (phloionic acid) is reported. The sodium derivative of 8-chloro-1-octyne couples with 6-iodo-1-chlorohexane to give 1,14-dichloro-7-tetradecyne. Application of the malonic ester synthesis to the corresponding 1,14-diiodo compound furnishes 9-octadecynedioic acid, which on semi-hydrogenation gives *cis*-9-octadecenedioic acid. Hydroxylation with performic acid forms phloionic acid; hydroxylation with permanganate forms the stereoisomer. The over-all yield of phloionic acid from 8-chloro-1-octyne is 25–29%.

Zetzsche and his co-workers[2,3] showed by degradation that phloionic acid, isolable from cork, has the structure of 9,10-dihydroxyoctadecanedioic acid (VII). The structure was confirmed when phloionic acid as well as its stereoisomer was synthesized by Ruzicka, *et al.*,[4] starting with 9-undecynoic acid, and again by Hunsdiecker,[5] starting with aleuritic acid (9,10,16-trihydroxypalmitic acid). In the present paper we described a new synthesis—starting with 8-chloro-1-octyne—which we have utilized to advantage for the preparation of phloionic acid (*cf.* formulations I–VII).

The first objective was the synthesis of 1,14-dichloro-7-tetradecyne (III) by the coupling of the sodium derivative of 8-chloro-1-octyne (I)[6,7] with 6-iodo-1-chlorohexane (II).

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(1) Abstracted from the dissertation submitted by Herbert N. Schlein in partial fulfillment of the requirements for the degree of Doctor of Philosophy in Boston University Graduate School.

(2) F. Zetzsche and M. Bahler, *Helv. Chim. Acta*, **14**, 846 (1931).

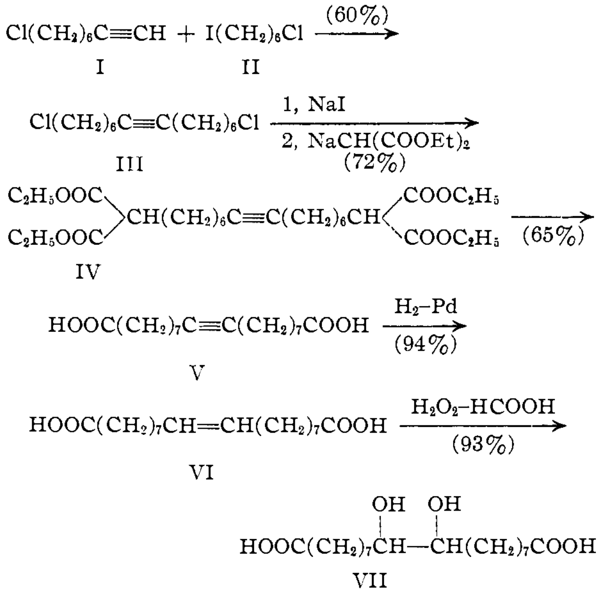
(3) F. Zetzsche and K. Weber, *J. prakt. Chem.*, **150**, 140 (1938).

(4) L. Ruzicka, Pl. A. Plattner and W. Widmer, *Helv. Chim. Acta*, **25**, 1086 (1942).

(5) H. Hunsdiecker, *Ber.*, **77**, 185 (1944).

(6) R. A. Raphael and F. Sondheimer, *J. Chem. Soc.*, 2100 (1950).

(7) W. J. Gensler and G. R. Thomas, THIS JOURNAL, **73**, 4601 (1951).



$$Cl(CH_2)_6C\equiv CH + I(CH_2)_6Cl \xrightarrow{(60\%)}$$

I II

$$Cl(CH_2)_6C\equiv C(CH_2)_6Cl \xrightarrow[2,\ NaCH(COOEt)_2 \quad (72\%)]{1,\ NaI}$$

III

$$(C_2H_5OOC)_2CH(CH_2)_6C\equiv C(CH_2)_6CH(COOC_2H_5)_2 \xrightarrow[(65\%)]{}$$

IV

$$HOOC(CH_2)_7C\equiv C(CH_2)_7COOH \xrightarrow[(94\%)]{H_2\text{-}Pd}$$

V

$$HOOC(CH_2)_7CH{=}CH(CH_2)_7COOH \xrightarrow[(93\%)]{H_2O_2\text{-}HCOOH}$$

VI

$$HOOC(CH_2)_7\overset{OH}{\overset{|}{C}}H\text{—}\overset{OH}{\overset{|}{C}}H(CH_2)_7COOH$$

VII

The reaction proceeded smoothly, but the product, as indicated by its infrared absorption, was contaminated with a terminal acetylenic compound.[8a] Pure 1,14-dichloro-7-tetradecyne could be obtained only after treatment of the coupling product with mercuric chloride and sodium ethoxide.[8b] Two alternate preparations of III, *viz.*, the reaction of two moles of 6-iodo-1-chlorohexane with sodium acetylide and sodamide, and the combination of two moles of 6-iodo-1-chlorohexane with acetylenedimagnesium bromide, proved unsatisfactory.

Alkylation of sodiomalonic ester was carried out with 1,14-diiodo-7-tetradecyne, which was prepared by treating the 1,14-dichloro compound III with sodium iodide in acetone. Alkylation with the diiodo compound was very much faster than with the dichloro compound, and the yield of tetraester IV was much higher. Saponification of tetraester IV gave the corresponding tetraacid, which on decarboxylation gave 9-octadecynedioic acid (V). That the triple bond had not migrated[9] under the influence of the basic conditions of alkylation or of saponification was shown by the production of azelaic acid on ozonolysis of the diacid V.

The palladium hydrogenation product formed by adding one mole of hydrogen to the highly purified acetylenic diacid V (m.p. 99–100°) was a mixture and not a single compound. In contrast, when the hydrogenation was performed *using somewhat less pure* acetylenic diacid V, hydrogen absorption stopped automatically at the half-hydrogenation mark, and 9-octadecenedioic acid (VI) was obtained in near quantitative yield. When catalyst recovered from the hydrogenation of less pure material was used as the catalyst for hydrogenation of highly purified material, hydrogenation again stopped short after absorption of one mole of hydrogen, and acid VI was formed again in high yield. It was clear that a highly effective but unidentified catalyst poison, present in the partially purified acetylene V, was lost during the processing leading to the pure (99–100°) material.

Formation of the double bond in 9-octadecenedioic acid by catalytic hydrogenation of a triple bond can be taken as evidence of a *cis* arrangement in VI.[10] This confirms the *cis* assignment made before for this acid (m.p. 69–70°) by comparing melting points of the two geometric forms.[4,5,11]

Phloionic acid (VII), m.p. 121–122°, was prepared by hydroxylating *cis*-9-octadecenedioic acid (VI) with hydrogen peroxide in formic acid.[15] The *threo* (racemic) configuration tentatively suggested before for phloionic acid[4,5] receives support from our preparation, since hydroxylation of a *cis*-olefin with peroxide produces the *threo*-glycol.[16] The synthetic phloionic acid did not depress the melting point of phloionic acid isolated from cork.[2,17] The *erythro* (*meso*) form of phloionic acid, m.p. 156–157°,[4,5] was prepared by hydroxylating *cis*-acid VI with alkaline permanganate.[18]

NOTE ADDED IN PROOF.—We are indebted to Dr. Ignacio Ribas of the Universidad de Santiago de Compostela for calling our attention to two recent articles: I, Ribas and E. Seoane [*Anales Real soc. españ. fis. y quim.* (Series B), 963 (1954)] isolated both *threo* (m.p. 124°) and *erythro* (m.p. 158°) 9,10-dihydroxyoctadecanedioic acids by hydroxylation of unsaturated cork acids with permanganate. Peracetic acid hydroxylation of the unsaturated acid fraction, which with permanganate formed the 158° material, gave the 124° acid. Evidently both *cis*- and *trans*-9-octadecenedioic acids occur in the acids from cork. G. Dupont, R. Dulou and J. Cohen [*Compt. rend.*, **240**, 875 (1955)] obtained *threo* (m.p. 121°) and *erythro* (m.p. 160°) dihydroxyoctadecanedioic acids by performic hydroxylation of *cis*- and of *trans*-9-octadecenedioic acid, respectively. We take this opportunity to report on the resolution (partial?) of phloionic acid, a result that unequivocally fixes the *threo* configuration for phloionic acid.

Thanks are due to Marguerite F. Syner who very kindly provided translations from the Spanish.

Acknowledgment.—We are indebted to Dr. F. W. Breuer of Armstrong Cork Co. for a generous gift of cork dust.

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[8] (a) This may have been 16-chloro-1,9-hexadecadiyne. The analytical figures for the coupling product before removal of terminal acetylenes corresponded closely to a mixture of 5 *M* per cent. of 16-chloro-1,9-hexadecadiyne and 95 *M* percentage of 1,14-dichloro-7-tetradecyne. (b) Removal of terminal acetylene compounds by precipitation with mercuric chloride and sodium ethoxide was suggested by a qualitative test given in Shriner and Fuson's, "Systematic Identification of Organic Compounds," 3rd edition, John Wiley and Sons, Inc., New York, N. Y., 1948, p. 109.

[9] *Cf.* T. L. Jacobs in R. Adams, "Organic Reactions," Vol. V, John Wiley and Sons, Inc, New York, N. Y., 1949, p. 13.

[10] Many examples are known. See *inter alia* the references given by K. N. Campbell and L. T. Eby, THIS JOURNAL, **63**, 216 (1941); and the chapter by H. A. Weidlich, "Sterischer Verlauf der Katalytischen Hydrierung," in Schwab's "Handbuch der Katalyse," Vol. VII, part 1, Springer-Verlag, Wien, 1943.

[11] *trans*-9-Octadecenedioic acid, melting close to 100°, has been prepared by several groups.[4,5,12,13] With the *cis*-acid VI now readily available, it may be pointed out, parenthetically, that application of Blomquist's cyclization scheme[12] to acid VI opens the way to the synthesis of natural *cis*-civetone[14] as originally planned by Ruzicka[4] and by Hunsdiecker.[5]

[12] A. T. Blomquist, R. W. Holley and R. D. Spencer, THIS JOURNAL, **70**, 34 (1948).

[13] P. C. Mitter and B. K. Bhattacharyya, *J. Indian Chem. Soc.*, **19**, 69 (1942).

[14] *Cf.* M. Stoll, J. Hulstkamp and A. Rouvé, *Helv. Chim. Acta*, **31**, 543 (1948).

[15] See D. Swern, G. N. Billen, T. W. Findley and J. T. Scanlan, THIS JOURNAL, **67**, 1786 (1945).

[16] *Cf.* D. Swern, in R. Adams, "Organic Reactions," Vol. VII, John Wiley and Sons, Inc., New York, N. Y., 1953, p. 379.

[17] A. Guillemonat and G. Cesaire, *Bull. soc. chim. France*, **792** (1949). Also *cf.* I. Ribas Marques and E. S. Bardenca, Spanish Patent 195,668 (1951) [*C. A.*, **47**, 6439 (1953)].

[18] *Cf.* J.-C. Traynard, *Bull. soc. chim. France*, 323 (1952).

Experimental[19]

1,14-Dichloro-7-tetradecyne (III).—8-Chloro-1-octyne (I) was formed in 95% yield by following essentially the published directions.[7] The boiling point was 88–92° (20 mm.) and the index of refraction (n^{25}D) was 1.4540–1.4544. Sodium fusion of this material followed by application of the standard qualitative test showed the presence of iodine, presumably because of the presence of 8-iodo-1-octyne.

A 1-liter three-necked flask was fitted with a reflux condenser cooled with solid carbon dioxide, a stirrer (mercury sealed) and a dropping funnel. A solution of sodamide in 600 ml. of liquid ammonia containing 1 g. of desiccated ferric nitrate was formed by adding a total of 3.5 g. (0.15 gram atom) of clean sodium. 8-Chloro-1-octyne (22 g. or 0.15 mole) was added rapidly to the gray-white suspension in the liquid ammonia, and the mixture was stirred under reflux for one hour. 6-Iodo-1-chlorohexane[6,7] (36 g. or 0.15 mole) then was added in one portion. The flask and dropping funnel were rinsed with 25 ml. of absolute ether, which was added to the liquid ammonia. The mixture was stirred under reflux for 4.5 hours.

Forty milliliters of water was added dropwise as fast as the capacity of the condenser permitted. This was followed by another 160 ml. of water. The solid carbon dioxide condenser was replaced with a water-cooled condenser, and the mixture was allowed to stand overnight at room temperature. Ordinary extraction in a separatory funnel was impractical since addition of ether to the concentrated aqueous ammonia solution resulted in a vigorous evolution of ammonia. Instead, peroxide-free ether (150 ml.) was added, and after the mixture was stirred for about ten minutes the ether layer was removed with a large pipet. This procedure was repeated with 100 ml. and with 75 ml. of peroxide-free ether. The combined ether extracts were washed successively with water, 4% sulfuric acid and twice with water. The ethereal solution was dried over sodium sulfate and the solvent was stripped; distillation in a Claisen flask until the vapors were at 130° (20 mm.) removed other low boiling materials.

The residue dissolved in 135 ml. of absolute alcohol was treated with a solution of 3 g. of sodium in 75 ml. of absolute alcohol. After five minutes, 5 g. of mercuric chloride was added. The resulting voluminous light yellow precipitate was removed by filtration through a sintered glass funnel of medium porosity. The precipitate was rinsed with 40 ml. of absolute alcohol, which was added to the main filtrate. Addition of more mercuric chloride (2.5 g.) produced more of the precipitate, which was removed as before. The filtrations were slow. Finally all alcohol was removed from the clear filtrate by evaporation under water-pump pressure.

The remaining orange-yellow oil was diluted with 450 ml. of petroleum ether (b.p. 30–60°), and the mixture was filtered and then extracted with three 75-ml. portions of 6 *N* hydrochloric acid, or until a test for mercuric ion with stannous chloride was negative. The petroleum ether solution, after washing with two 50-ml. portions of water, was dried with sodium sulfate. Removal of solvent followed by two distillations in a Claisen still gave 23.6 g. (60%) of water-white 1,14-dichloro-7-tetradecyne (III) with n^{25}D 1.4784 and b.p. 124–125° (0.3 mm.).

Anal. Calcd. for $C_{14}H_{24}Cl_2$: C, 63.9; H, 9.2. Found: C, 64.1; H, 9.4.

This product showed no acetylenic hydrogen absorption in the infrared. Yields of pure materials as high as 71% were obtained by the above procedure.

Removal of terminal acetylenic impurities by distillation, or by precipitations with ammoniacal silver nitrate, with ammoniacal copper sulfate, or with alcoholic mercuric iodide and sodium ethoxide was not satisfactory.

1,1,16,16-Tetracarbethoxy-8-hexadecyne (IV).—A solution of 34 g. (0.13 mole) of 1,14-dichloro-7-tetradecyne (III) in 500 ml. of acetone was treated with 60 g. (0.40 mole) of sodium iodide dissolved in 500 ml. of acetone. The yellow mixture was stirred and boiled for 54 hours. At the end of this period most of the acetone was removed from the mixture, now red, by distillation directly from the reaction flask. Stirring was continued to prevent bumping. Water (250 ml.) was added to dissolve the salts, and the mixture was extracted with 300 ml. of peroxide-free ether. The ether solution was washed with 75 ml. and then with 25 ml. of 10% sodium thiosulfate solution. The red color changed to yellow. Contact time between the ether and the thiosulfate solution was kept to a minimum. After washing the ether with two 150-ml. portions of water, the ether was dried over magnesium sulfate and finally removed by distillation up to 100°. 1,14-Diiodo-7-tetradecyne (58.0 g. or 100% yield) was left as residual oil. Since experience had shown that distillation of the diiodo compound even under high vacuum was accompanied by extensive decomposition the material was used without further purification.

Absolute alcohol was distilled over calcium hydride directly into a two-necked flask protected from atmospheric moisture. Clean sodium (6.2 g. or 0.27 gram atom) was dissolved in this alcohol (250 ml.) and 48 g. (0.30 mole) of freshly distilled ethyl malonate was added. The diiodo compound (58 g. or 0.13 mole) then was added in one portion, and the mixture was shaken, allowed to stand at room temperature for 20 minutes, and finally refluxed for 15 minutes. Titration of small aliquots taken at frequent intervals from the reaction mixture showed that the reaction was substantially complete after 15 minutes at room temperature.

Unreacted ethoxide was neutralized with the calculated amount of concentrated hydrochloric acid, and the ethanol was removed by distillation on the steam-bath. Water (150 ml.) and peroxide-free ether (100 ml.) were added to the mixture of liquid and solid. The organic layer was separated, and was washed successively with water, 2% sodium bisulfite solution (100 ml.), and twice with water. After drying the ethereal solution over magnesium sulfate, solvent and unreacted ethyl malonate were removed by distillation to a boiling point of 83° (1 mm.). The red residual oil was distilled in small batches in a creased tube to give 48 g. (72%) of light yellow tetraester IV, b.p. (bath) 160° at 10 μ, and n^{25}D 1.4740. A sample for analysis was prepared by a second distillation, which furnished pale yellow product (n^{25}D 1.4759) in 90% recovery.

Anal. Calcd. for $C_{28}H_{46}O_8$: C, 65.9; H, 9.1. Found: C, 65.9; H, 9.4.

9-Octadecynedioic Acid (V).—A solution of once-distilled tetraester (38.8 g. or 0.076 mole) in 300 ml. of 75% (volume) ethanol containing 90 g. (2.25 moles) of sodium hydroxide was boiled under reflux for four hours. After the mixture was concentrated by distilling solvent on the steam-bath, water (150 ml.) was added and the mixture extracted with two 50-ml. portions of ether. The ether was washed with 100 ml. of water and the wash water returned to the aqueous phase. Concentrated hydrochloric acid was added until the *p*H was approximately 2, and the acid mixture was extracted with ether. The extract was washed twice with water and was dried over sodium sulfate. Solvent and all volatile material was removed from the dried ether solution by flash distillation in a 250-ml. still and by exposure of residual solid 1,1,16,16-tetracarboxy-8-hexadecyne to a water-pump vacuum at a temperature of 65° until the flask reached constant weight.

(In other experiments the tetraacid was collected at this point. The yield was always greater than 90%. The observed neutralization equivalent of the somewhat waxy product (104–105) was a little higher than the theoretical (99.6). Although ethyl acetate appeared to be a satisfactory solvent, no purification prior to decarboxylation was attempted.)

The flask, evacuated to 8 μ, was heated in a bath at 180°. Gas evolution from the yellowish mass was vigorous. During the 30-minute heating period, the weight loss was 6.55 g. or 98% of the value calculated for loss of two moles of carbon dioxide. The red decarboxylation product was extracted with seven 100-ml. portions of boiling petroleum ether (b.p. 60–90°). The combined petroleum ether solutions, on cooling overnight at 0°, deposited yellow, somewhat waxy 9-octadecynedioic acid (V), m.p. 82–89°. Recrystallization from 500–600 ml. of petroleum ether (b.p. 60–90°) afforded 15.3 g. (65% from the tetraester) of faintly yellow acid V, m.p. 95–99°, which was suitable for use in the next step. Three crystallizations from petroleum ether brought the melting point to 99–100°; a fourth crystallization did not raise the melting point.

Anal. Calcd. for $C_{18}H_{30}O_4$: C, 69.6; H, 9.7; neut. equiv., 155. Found: C, 69.8; H, 10.0; neut. equiv., 154, 156.

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[19] Analyses were performed by Carol K. Fitz, Ph.D., 115 Lexington Ave., Needham Heights 94, Mass. All melting points are corrected.

Ozonolysis of 9-Octadecynedioic Acid (V).—Ozonized oxygen in excess was passed through an acetic acid solution (60 ml.) of V (75 mg.), m.p. 99–100°, at room temperature. After evaporation of approximately 50 ml. of the solvent in a current of dry nitrogen at temperatures no higher than 45°, 10 ml. of 30% hydrogen peroxide (Merck Superoxol) and 5 ml. of water were added, and the mixture was allowed to stand overnight at room temperature. The azelaic acid cleavage product, after isolation and crystallization from water and from ethyl acetate, melted alone or admixed with authentic azelaic acid at 105–106°. The yield was 74 mg. or 81%.

***cis*-9-Octadecenedioic Acid (VI) from 9-Octadecynedioic Acid (V).**—A solution of 6.2 g. (0.020 mole) of 9-octadecynedioic acid (melting a few degrees lower than the analytical sample) in 170 ml. of absolute methanol containing 150 mg. of 10% palladium-on-carbon that had been saturated previously with hydrogen was stirred at room temperature under one atmosphere of hydrogen. Hydrogen corresponding to 98% of the theoretical for one mole was absorbed after one-half hour. No further absorption was evident after another 15 minutes of stirring. The catalyst was removed by filtration through a sintered glass funnel and was washed with two small portions of absolute methanol. Removal of all solvent from the combined filtrates by evaporation in a stream of dry nitrogen at room temperature left 6.18 g. of a white solid, m.p. 67–68°. Two crystallizations of this material from ethyl acetate gave 4.3 g. of product, m.p. 69–70°. Reworking the mother liquors gave an additional 1.6 g. with the same melting point. The total yield of *cis*-acid VI was 94%.

Anal. Calcd. for $C_{18}H_{32}O_4$: C, 69.2; H, 10.3; neut. equiv., 156. Found: C, 69.3; H, 10.3; neut. equiv., 156.

Phloionic Acid (VII) from *cis*-9-Octadecenedioic Acid.[15]—To a solution of 6.2 g. (0.020 mole) of 9-octadecenedioic acid in 40 ml. of 98–100% formic acid was added 3 ml. of aqueous hydrogen peroxide containing 0.023 mole of peroxide by iodimetric titration. An exothermic reaction was noted. The flask was kept for one hour in a 40° water-bath.

The reaction mixture was poured into 150 ml. of 4 *N* sodium hydroxide solution, and the solution was boiled for one-half hour. Concentrated hydrochloric acid was added to bring the *p*H to 2, and the acid solution was allowed to stand at 0° for 18 hours. The solids were collected by filtrations, washed with cold water and air-dried. Two crystallizations from ethyl acetate raised the melting points from 114–117° to 121–122°, and afforded 6.4 g. (93%) of phloionic acid. A third crystallization did not change the melting point.

Anal. Calcd. for $C_{18}H_{34}O_6$: C, 62.4; H, 9.9; neut. equiv., 173. Found: C, 62.2; H, 10.0; neut. equiv., 173, 175.

The melting point of a mixture of this synthetic phloionic acid with phloionic acid isolated from cork (*vide infra*) was 120.5–122°.

***meso*-9,10-Dihydroxyoctadecanedioic Acid (VII) from *cis*-9-Octadecenedioic Acid (VI).**[18]—A solution of 3.1 g. (0.010 mole) of acid VI in 20 ml. of water containing 1 g. of potassium hydroxide was cooled to 5°, finely powdered potassium permanganate (1 g. or 0.0063 mole) was added, and the mixture was allowed to stand without cooling for ten minutes. Sulfur dioxide was bubbled into the mixture until all the precipitated manganese dioxide dissolved. The resulting mixture (*p*H 4) was cooled, and the white precipitate was collected on the funnel, washed with 4 ml. of cold water, and dried by drawing air through the funnel. The crude product was boiled with 40 ml. of ethyl acetate, and the hot solution gravity filtered to remove some insoluble material. The filtrate, kept at 0°, deposited 1.9 g. of white crystals, m.p. 152–155°. Two additional crystallizations from ethyl acetate (25 and 20 ml.) gave 1.54 g. of material melting at 156–157°. Another crystallization did not change the melting point.

Anal. Calcd. for $C_{18}H_{34}O_6$: C, 62.4; H, 9.9; neut. equiv., 173. Found: C, 62.5; H, 10.1; neut. equiv., 173, 177.

The total yield of *erythro*-9,10-dihydroxyoctadecanedioic acid, m.p. 156–157°, including material obtained on reworking mother liquors, was 1.91 g. (55%).

Phloionic Acid (VII) from Cork.—Isolation of phloionic acid from cork was carried out as described by Guillemonat and Cesaire[17] except that the dry mixture of phloionic acid and calcium sulfate (from 500 g. of powdered cork) was continuously extracted in a Soxhlet apparatus with 350 ml. of ethyl acetate for two days. The extract was concentrated to 200 ml. by distillation, and was cooled first to room temperature and then to 0° where it was held for two days. The precipitate (8.6 g., m.p. 115–119°) was collected and was recrystallized twice from ethyl acetate. Decolorizing carbon (Darco G-60) was used in one of the crystallizations. Phloionic acid (5.43 g.) was obtained in this way as white platelets, m.p. 121–122°. Reworking mother liquors gave an additional 0.48 g. with the same melting point; neut. equiv., calcd., 173; found, 172, 177.

Other isolation experiments starting with 500-g. batches of cork dust afforded 6.8, 7.0 and 7.2 g. of phloionic acid, m.p. 121–122°.

BOSTON, MASSACHUSETTS

[CONTRIBUTION FROM THE COLLEGE OF PHARMACY, UNIVERSITY OF MICHIGAN]

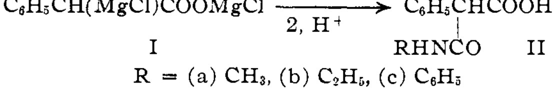
The Reaction of the Chloromagnesium Derivative of Chloromagnesium Phenylacetate with Isocyanates, Carbamyl Chlorides and Isothiocyanates

BY F. F. BLICKE AND HAROLD ZINNES[1,2]

RECEIVED MAY 18, 1955

The Ivanov reagent, obtained from phenylacetic acid and isopropylmagnesium chloride, reacted with isocyanates and carbamyl chlorides to yield N-substituted α-phenyl-α-carbamylacetic acids. The products isolated when the Ivanov reagent reacted with isothiocyanates were N-substituted thioamides of phenylacetic acid.

Since it is known that the common type Grignard reagents react with isocyanates,[3] it was to be expected that the Ivanov reagent, $C_6H_6CH(MgCl)$-$COOMgCl$ (I), prepared from phenylacetic acid and isopropylmagnesium chloride, would react with isocyanates in the manner indicated below. By interaction of compound I with isocyanates, three N-substituted α-phenyl-α-carbamylacetic acids (II) were obtained; they were converted into their methyl esters.



$$\underset{\mathrm{I}}{\mathrm{C_6H_5CH(MgCl)COOMgCl}} \xrightarrow[2,\ H^+]{1,\ \mathrm{RNCO}} \underset{\mathrm{RHNCO}}{\mathrm{C_6H_5\underset{|}{C}HCOOH}} \quad \mathrm{II}$$

R = (a) CH_3, (b) C_2H_5, (c) C_6H_5

The Ivanov reagent I reacted with diethylcarbamyl chloride and with diphenylcarbamyl chloride to form α-phenyl-α-(diethylcarbamyl)-acetic (III)

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[1] This paper represents part of a dissertation submitted by Harold Zinnes in partial fulfillment of the requirements for the Ph.D. degree in the University of Michigan, 1955.

[2] American Foundation for Pharmaceutical Education Fellow.

[3] See M. S. Kharasch and O. Reinmuth, "Grignard Reactions of Nonmetallic Substances," Prentice-Hall, Inc., New York, N. Y., 1954, p. 1199.