The *cis* form proves to have a higher heat content than the *trans*, heat being evolved in changing from the former to the latter. The difference is not far from that predicted by the earlier work,[3] but the degree of certainty is very much improved.

There is obviously very little resonance energy in decalin, as may be shown by comparison of the heat of formation from gaseous carbon and atomic hydrogen with the bond energy of 18 C–H bonds and 11 C–C bonds using the values of Pauling.[9]

Bond energy, either form, 2215.0 kcal.; calculated heat of formation in gaseous state from gaseous atoms *cis*- −2215.8; *trans*- −2218.0 kcal. Utilized in these latter calculations is the latent heat of vaporization (10.5 kcal. mole^{-1}) taken from the data of Hertz.[10] The low energy of isomerization moreover ties in with the observation that aluminum chloride at room temperature catalyzes the change *cis* → *trans*.[11]

G. F. D. is indebted to the Standard Oil Company of California for a Fellowship during the tenure of which this work was carried out. Grateful acknowledgment is also due to the Cyrus M. Warren Fund of the American Academy of Arts and Sciences for funds used in the purchase of equipment.

(9) L. Pauling, "The Nature of the Chemical Bond," Cornell University Press, Ithaca, N. Y., 1939.

(10) Hertz, *Z. physik. Chem.*, **101**, 269 (1922).

(11) Zelinskii and Turnova-Pollak, *Ber.*, **65B**, 1299 (1932).

Summary

1. The isothermal heats of combustion of *cis*- and *trans*-decahydronaphthalene have been determined at 25°.

2. The standard heat of formation and the heat of isomerization of the two forms have been calculated.

CORVALLIS, OREGON RECEIVED MARCH 3, 1941

[CONTRIBUTION FROM THE COBB CHEMICAL LABORATORY, UNIVERSITY OF VIRGINIA]

The Synthesis of Some Iodinated Aromatic Compounds

BY LOUIS LONG, JR.,[1] AND ALFRED BURGER

The application of iodine compounds to clinical X-ray visualization and chemotherapy[2] has prompted the preparation of a series of aromatic iodine derivatives for biological experimentation.

On the assumption that a high percentage of iodine was desirable in these compounds, preliminary attempts have now been made to prepare derivatives of 2,4,6-triiodoaniline of possible therapeutic value. As the sulfanilamide derivative was considered interesting for this purpose, 2,4,6-triiodoaniline was treated with N-acetylsulfanilyl chloride under various conditions in different solvents, including dry pyridine, pyridine and acetone, dimethylaniline, and quinoline, but only starting material was recovered. The failure of the reaction is assumed to be the result of steric hindrance similar to that of other ortho substituted amines. In like manner, attempts to make 2,4,6-triiodophenylglycine, using formaldehyde and potassium cyanide,[3] ethyl iodoacetate, or ethyl iodoacetate with pyridine in chlorobenzene as a solvent, gave none of the desired compound. Another trial designed to prepare 2,4,6-triiodophenylurea, using nitrourea and 95% ethanol,[4] was also unsuccessful. It was found possible, however, to form 2,4,6-triiodoacetanilide with acetic anhydride and a drop of concentrated sulfuric acid. Like picramide, 2,4,6-triiodoaniline crystallized unchanged from acetic anhydride, and the addition of sulfuric acid was necessary to catalyze the reaction.

More reactive iodinated starting materials were found in 2,4-diiodoaniline[5] and 2,4,6-triiodophenol. N^4-Acetyl-N^1-2,4-diiodophenylsulfanilamide was made in good yield, and the corresponding N^1-2,4-diiodophenylsulfanilamide was obtained readily on hydrolysis with alcoholic hydrogen chloride. 2,4-Diiodophenylglycine could be made in only very low yield by the two methods tried for the formation of 2,4,6-triiodophenylglycine. Better results were obtained from the iodination of phenylglycine by the method of Waters,[5] which yielded reasonable amounts of the desired compound. Difficulties were also encountered in the preparation of 2,4-diiodophenylurea. It was necessary to add pyridine to decompose the nitrourea at room temperature, as

(1) Smith, Kline and French Research Fellow.

(2) "New and Nonofficial Remedies," American Medical Association, Chicago, Ill., 1940, pp. 226, 289, 300, 302, 304.

(3) Schwalbe, Schulz, and Jochheim, *Ber.*, **41**, 3790 (1908).

(4) Buck and Ferry, THIS JOURNAL, **58**, 854 (1936).

(5) Waters, *J. Chem. Soc.*, 1060 (1933).

the low basicity of the amine prevented the application of the usual method. Iodination of phenylurea gave only *p*-iodophenylurea.

2,4,6-Triiodophenoxyacetic acid was prepared readily by the reaction of sodium 2,4,6-triiodophenolate with ethyl chloroacetate, or ethyl iodoacetate, in absolute ethanol. A series of dialkylaminoalkyl ethers of 2,4,6-triiodophenol was also made with reasonable yields. By application of the Williamson ether synthesis sodium 2,4,6-triiodophenolate was condensed with 1-diethylamino-2-chloroethane, 1-diethylamino-3-chlorobutane, and 1-diethylamino-3-chloropentane to yield 1-diethylamino-2-(2,4,6-triiodophenoxy)-ethane, 1-diethylamino-3-methyl-3-(2,4,6-triiodophenoxy)-propane, and 1-diethylamino-3-ethyl-3-(2,4,6-triiodophenoxy)-propane, respectively. Due to the short life of the free tertiary amines[6] it was necessary to bring the amine into reaction as soon as possible after its liberation from the hydrochloride.

Experimental[7]

2,4,6-Triiodoacetanilide.—Three drops of concentrated sulfuric acid were added to a mixture of 0.3 g. of 2,4,6-triiodoaniline and 2 cc. of acetic anhydride. The material went into solution with spontaneous heating, and crystals appeared after a short time. The mixture was heated at 80° for two minutes, allowed to cool, the crystalline precipitate was filtered, pressed well, and recrystallized from 40 cc. of boiling glacial acetic acid. Triiodoacetanilide crystallized as colorless needles, m. p. 276–277° (dec.).

Anal. Calcd. for $C_8H_6I_3NO$: C, 18.73; H, 1.18. Found: C, 18.48; H, 1.48.

A similar reaction, using chloroacetic anhydride, caused decomposition of the material.

N^4-Acetyl-N^1-2,4-diiodophenylsulfanilamide.—To a solution of 9.8 g. of 2,4-diiodoaniline[9] in 50 cc. of dry pyridine was added 9.8 g. of N-acetylsulfanilyl chloride in six portions with intermittent cooling. After standing for one hour at room temperature, the flask was heated for twenty hours on the steam-bath. The dark brown pyridine solution was added dropwise to 110 cc. of 18% hydrochloric acid at 0° with mechanical stirring. A white precipitate separated which was collected after standing for several hours and washed with water. For purification, the product was dissolved in 30 cc. of hot 2 *N* sodium carbonate solution, and, after filtration, reprecipitated with 2 *N* hydrochloric acid to yield 12.0 g. (78%) of crude material. Two crystallizations from 95% ethanol with Norit gave colorless needles, m. p. 230–231°.

Anal. Calcd. for $C_{14}H_{12}I_2N_2O_3S$: C, 31.02; H, 2.23. Found: C, 31.25; H, 2.36.

N^1-2,4-Diiodophenylsulfanilamide.—A mixture of 7.0 g. of N^4-acetyl-N^1-2,4-diiodophenylsulfanilamide, 100 cc. of 95% ethanol and 30 cc. of concentrated hydrochloric acid was boiled under reflux for one hour. The resultant solution was poured into 500 cc. of water, and made weakly alkaline with ammonium hydroxide. The precipitate formed was purified by two crystallizations from 95% ethanol, and yielded 4.5 g. (70%) of glistening pale yellow needles, m. p. 176–178°.

Anal. Calcd. for $C_{12}H_{10}I_2N_2O_2S$: C, 28.82; H, 2.02. Found: C, 28.61; H, 2.32.

2,4-Diiodophenylglycine.—(a)[8] To a mixture of 1.0 g. of 2,4-diiodoaniline, 0.3 g. of 95% ethanol, 0.01 g. of 30% potassium hydroxide solution, and 0.12 g. of 40% formaldehyde heated to 80° was added 0.2 g. of boiling 49% aqueous potassium cyanide, and boiling under reflux was continued for three hours. After cooling to room temperature, 10 cc. of water was added and undissolved 2,4-diiodoaniline was removed by filtration. The filtrate was extracted with chloroform and ether, and yielded a white amorphous precipitate of 2,4-diiodophenylglycine on acidification with concentrated hydrochloric acid. Crystallization from water gave 25 mg. (2.1%) of colorless needles, m. p. 160–160.5° (dec.).

Anal. Calcd. for $C_8H_7I_2NO_2$: C, 23.84; H, 1.75. Found: C, 24.09; H, 1.98.

(b) A solution of 1.0 g. of 2,4-diiodoaniline, 0.62 g. of ethyl iodoacetate, and 0.23 g. of dry pyridine in 13 cc. of absolute ethanol was refluxed for seventeen hours, the ethanol was removed in vacuum, and the residual deep red oil dissolved in 15 cc. of chloroform. After extraction with 10% hydrochloric acid, *N* sodium thiosulfate, and water, and drying over anhydrous sodium sulfate, the chloroform was removed in vacuum. The residual crystalline material was recrystallized from ethanol–water and methanol to give 0.45 g. of light tan blades, m. p. 70–90°, assumed to be a mixture of ethyl 2,4-diiodophenylglycinate with 2,4-diiodoaniline, m. p. 94–95°. The ester was hydrolyzed by refluxing with 0.08 g. of potassium hydroxide in 6 cc. of absolute ethanol for two hours. The solvent was removed, the residue extracted with water, and 50 mg. (4.2%) of 2,4-diiodophenylglycine, m. p. 156–158° (dec.), was liberated by acidification.

The yield of crude glycine was doubled in another experiment in which dry chlorobenzene was used as a solvent instead of absolute ethanol, but the product was less pure.

(c)[5] Four grams of phenylglycine was dissolved in 120 cc. of 95% ethanol, and 20 cc. of concentrated hydrochloric acid was added at 0°. To this solution was added dropwise at 0–5° with mechanical stirring a solution of 6.25 g. of potassium iodate and 5.86 g. of potassium iodide in 175 cc. of water. The resultant black mixture was treated with a suspension of ice, water and 100 cc. of 5% sodium sulfite solution made up to a volume of about 500 cc. After allowing the emulsion to stand overnight, the supernatant liquid was decanted, the black solid residue washed with a little ice-cold water by decantation, collected by suction filtration, washed again and dried. The crude material weighed 9.5 g., m. p. 120–140° (dec.).

For purification, the dark amorphous powder was dissolved in 100 cc. of 5% sodium bicarbonate solution, boiled with Darco, filtered hot, and the acid reprecipitated from the filtrate with 10% hydrochloric acid. The light yellow powder obtained after repeating the above procedure

(6) Marvel, Zartman and Bluthardt, THIS JOURNAL, **49**, 2299 (1927).

(7) Microanalyses by Mrs. Elizabeth Johnson Mathers.

weighed 3.0 g. (28%), m. p. 149–150° (dec.). After three crystallizations from benzene, the substance formed colorless needles, m. p. 161–162° (dec.), which did not depress the melting point of the analytical sample made by method (a).

2,4-Diiodophenylurea.—As the procedure of Buck and Ferry[4] failed to yield the desired compound, certain modifications were introduced to circumvent the low basicity of 2,4-diiodoaniline.

6.99 grams of 2,4-diiodoaniline was dissolved in 125 cc. of 95% ethanol and 10 cc. of pyridine, and 2.52 g. of nitrourea[8] was added. After standing at room temperature for twenty-four hours, the nitrourea had disappeared and a small amount of crystalline material had separated. This substance was collected, 2.52 g. of nitrourea was added to the filtrate, and the mixture was left at room temperature for twenty-four hours. The process was repeated until four additions of 2.52 g. of nitrourea had been made. In this manner, 750 mg. of crude product was collected. Two crystallizations from 95% ethanol, recrystallization from acetone, and sublimation at 2 mm. and 250° gave 50 mg. of colorless microneedles, m. p. 294–295° (dec.).

Anal. Calcd. for $C_7H_6I_2N_2O$: C, 21.67; H, 1.56. Found: C, 22.23; H, 1.63.

The filtrate from the above crude product was concentrated to 10 cc., and 1.0 g. of a second crystalline product was obtained on cooling, m. p. 175–176°. Crystallization from 95% ethanol, and acetone gave 0.79 g. of colorless blades, m. p. 188–189°. The compound was analyzed, but no formula could be deduced from the data, and further work was not undertaken.

Anal. Found: C, 36.42; H, 6.28.

Fractional crystallization of the mother liquors of this compound yielded 2.0 g. of 2,4-diiodophenylurea and 1.5 g. of 2,4-diiodoaniline. The total yield of 2,4-diiodophenylurea was 2.3 g. (29%).

2,4,6-Triiodophenoxyacetic Acid.—Seven grams of 2,4,6-triiodophenol was dissolved in a solution of 0.63 g. of sodium in 60 cc. of butanol. Addition of 5 g. of ethyl chloroacetate caused immediate formation of a precipitate. The mixture was boiled under reflux for six hours with frequent agitation to prevent vigorous bumping of the increasing precipitate. After standing overnight, 20 cc. of a 30% sodium hydroxide soluion was added, and saponification of the ethyl ester was completed by heating for one hour. Water was added, and the solution was concentrated until sodium triiodophenoxyacetate began to separate. The salt was filtered after cooling, suspended in water, and triiodophenoxyacetic acid was liberated by acidification. Recrystallization from ethanol yielded colorless needles, m. p. 224–225° (dec.). The yield was 5.8 g. (74%).

Anal. Calcd. for $C_8H_5I_3O_3$: C, 18.13; H, 0.95. Found: C, 18.01; H, 1.02.

The sodium salt was sparingly soluble. Recrystallization from 50 parts of boiling water furnished colorless crystals.

Anal. Calcd. for $C_8H_4I_3NaO_3$: Na, 4.17. Found: Na, 4.13.

1-Diethylamino-2-(2,4,6-triiodophenoxy)-ethane.—A solution of 1.9 g. of sodium in 100 cc. of absolute ethanol was treated with 19.0 g. of 2,4,6-triiodophenol, and a solution of 7.0 g. of β-diethylaminoethyl chloride[9] in 20 cc. of absolute ethanol was added. Sodium chloride precipitated at once. The mixture was boiled under reflux for three hours, the solvent removed under reduced pressure, the residue dissolved in water and ether, and the ether solution washed repeatedly with a 10% sodium hydroxide solution. The oily residue from the ether solution was dissolved in 30 cc. of acetone, and the solution was neutralized with alcoholic hydrogen chloride. The hydrochloride crystallized immediately; the yield was 10.4 g. (42.6%). Recrystallization from methanol–ether rendered colorless blades, m. p. 195–196° (dec.).

Anal. Calcd. for $C_{12}H_{17}ClI_3NO$: C, 23.72; H, 2.82. Found: C, 23.55; H, 2.80.

The hydrochloride was soluble in about twenty parts of water. The base was liberated from the hydrochloride by addition of a sodium carbonate solution, and extracted into ether. It formed a colorless viscous oil which did not crystallize. The *picrate* formed quickly in ethanol solution and was recrystallized from ethanol; yellow crystals, m. p. 146–148° (dec.).

Anal. Calcd. for $C_{18}H_{19}I_3N_4O_8$: N, 7.00. Found: N, 7.07.

1-Diethylamino-3-methyl-3-(2,4,6-triiodophenoxy)-propane.—A solution of 2.1 g. of 1-diethylamino-3-chlorobutane hydrochloride[10] in 10 cc. of a saturated sodium chloride solution was made alkaline with potassium hydroxide, the base was extracted several times into ether, the combined ether extracts were dried over anhydrous sodium sulfate, and the ether was removed rapidly under reduced pressure at 30°. The colorless oily residue was dissolved in 5 cc. of absolute ethanol and added immediately to a solution of 5 g. of 2,4,6-triiodophenol in a solution of 0.25 g. of sodium in 20 cc. of absolute ethanol. The mixture was boiled for six hours, allowed to stand overnight, and the solvent was distilled under reduced pressure. The residue was worked up as described above for compound VI. The hydrochloride of the base was recrystallized from cold methanol–ether. It appeared as colorless needles, m. p. 190° (dec.). The yield was 4.2 g. (62%).

Anal. Calcd. for $C_{14}H_{21}ClI_3NO$: C, 26.45; H, 3.33. Found: C, 26.23; H, 3.56.

From the alkaline washings of the base, 1.1 g. of impure triiodophenol was recovered by acidification.

1-Diethylamino-3-ethyl-3-(2,4,6-triiodophenoxy)-propane.—Four and five-tenths grams of 1-diethylamino-3-chloropentane hydrochloride[10] was converted to the free base as described above in the case of diethylaminochlorobutane. A solution of the base in 10 cc. of absolute ethanol was added immediately to a solution of 7.8 g. of 2,4,6-triiodophenol in 30 cc. of absolute ethanol containing 0.4 g. of sodium. The mixture was boiled under reflux for four hours, the solvent was evaporated under reduced pressure, and the residue was worked up in the manner described above. The oily phenyl ether base yielded a mixture of hydrochlorides from which 1.1 g. of a sparingly soluble crystalline portion was isolated by washing with

(8) Davis and Blanchard, THIS JOURNAL, 51, 1790 (1929).

(9) Kindly furnished by Dr. J. S. Pierce, University of Richmond.

(10) Kindly supplied by Professor H. B. Hass and Dr. H. C. Huffman of Purdue University.

acetone. It was recrystallized from methanol–ether and appeared as colorless needles, m. p. 188–190° (dec.).

Anal. Calcd. for $C_{15}H_{23}ClI_3NO$: C, 27.73; H, 3.57. Found: C, 27.63; H, 3.85.

The acetone mother liquors of the hydrochloride deposited colorless crystals of another hydrochloride on standing, which melted at 160–170° (dec.). This compound could not be purified further.

2,4,6-Triiodophenyl Chloroacetate.—A solution of 2.9 g. of 2,4,6-triiodophenol and 3 g. of chloroacetic anhydride in 10 cc. of pyridine was allowed to stand overnight and then poured into 100 cc. of water. A crystalline precipitate and a brown tar were formed; the latter went slowly into solution. The crystals were filtered, washed, and recrystallized from boiling ethanol. The product crystallized as shining blades, m. p. 141–142°.

Anal. Calcd. for $C_8H_4ClI_3O_2$: C, 17.52; H, 0.74. Found: C, 17.76; H, 1.19.

Summary

2,4-Diiodophenylsulfanilamide, 2,4-diiodophenylglycine and 2,4-diiodophenylurea have been prepared from 2,4-diiodoaniline. A series of 2,4,6-triiodophenyl dialkylaminoalkyl ethers has also been synthesized. The failure of 2,4,6-triiodoaniline to take part in certain reactions has been discussed.

A study of the application of several of these compounds to X-ray visualization and chemotherapy is in progress.

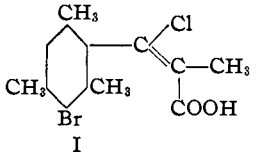
UNIVERSITY, VIRGINIA RECEIVED JANUARY 29, 1941

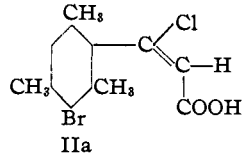
[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

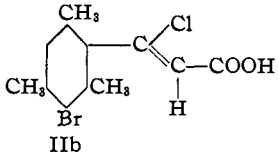
Restricted Rotation in Aryl Olefins. II. Preparation and Resolution of Certain β-Chloro-β-(2,4,6-trimethyl- and 2,4,6-triethyl-3-bromophenyl)-acrylic Acids

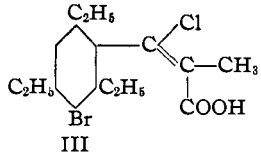
BY ROGER ADAMS, A. W. ANDERSON[1] AND M. W. MILLER[1]

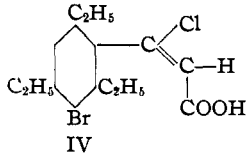
The observation that β-chloro-β-(2,4,6-trimethyl-3-bromophenyl)-α-methylacrylic acid (I) could be resolved and that the optically active forms were very stable to racemization was reported in a previous paper.[2] The study of several analogous compounds now has been completed; they are shown by formulas II–VII.

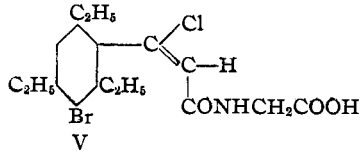

I


IIa


IIb

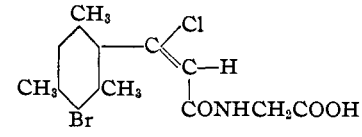

III

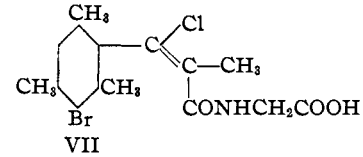

IV


V

(1) An abstract of a thesis submitted in partial fulfillment of the requirements for the degree of Doctor of Philosophy in Chemistry. Eastman Kodak Fellows, 1939–1940, 1940–1941.

(2) Adams and Miller, THIS JOURNAL, **62**, 53 (1940).


VI


VII

Compounds I and II differ merely by a methyl and hydrogen in the α-position to the carboxyl group. Compound I showed no signs of racemization after boiling for fifteen hours in ethanol or *n*-butanol. Compound II, on the other hand, though stable in boiling ethanol, slowly racemized in boiling *n*-butanol with a half-life of approximately two hundred minutes. Geometric forms of compound I and compound II theoretically are capable of existence but only a single form was isolated in either case and all attempts to prepare the isomers failed. It is reasonable to assume that molecules I and II have the same configuration.

The active isomers of the *cis*- and *trans*-forms (IIa and IIb) should have a marked difference in optical stability, for molecule IIa resembles more closely a 2,2′,6,6′-tetrasubstituted biphenyl and IIb a trisubstituted biphenyl. The latter are decidedly more labile than the former and in aryl