weight on exposure to air (presumably absorbing water vapor) but did not appear otherwise altered. The analysis of this sample showed: C, 33.40; H, 2.08; N, 56.68; Cl, 0.0; total, 92.16. Assuming the difference from 100% to be oxygen from absorbed water, the analysis on a dry basis becomes: C, 36.6; H, 1.2; N, 62.2. This percentage composition corresponds very well to that given by Franklin[2] and Laurent and Gerhardt[3] for the compound melon. In fact, the color, solubility, and non-melting of the compound fit the data on melon[4] quite well.

The formula assigned to melon[4] is $C_6N_9H_3$. From the amount of water absorbed by the sample analyzed one calculates the formula of the water containing substance to be $C_6N_9H_3 \cdot 1.01H_2O$—or closely one water molecule per molecule of melon.

The equation for the formation of melon is

$$6CCl_4 + 9NH_4Cl = C_6N_9H_3 + 33HCl$$

It is striking in that almost all of the bonds in the initial compounds are eventually broken to be replaced by carbon–nitrogen bonds. Most probably there is a series of intermediates involved in this extensive rupture and reconstitution of bonds. It is further of interest to note that when chloroform and ammonium chloride were heated together no reaction occurred, except decomposition of the chloroform.

(2) E. C. Franklin, THIS JOURNAL, **44**, 506 (1922).

(3) Laurent and Gerhardt, *Ann. chim.*, [3] **19**, 89 (1847).

(4) Beilstein, "Handbuch der organischen Chemie," 4th ed., Vol. III, 1921, p. 169.

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Cyclobutane Derivatives. V. Ziegler Bromination of Cyclobutene[1]

BY E. R. BUCHMAN AND D. R. HOWTON

Our interest in the cyclobutadiene problem[2] has led us to investigate the Ziegler bromination[3] of cyclobutene. Orienting experiments carried out accoring to Ziegler[4] gave only traces of allylic bromide. The optimum conditions[5] for bromination of the related methylenecyclobutane, when applied to cyclobutene, yielded about 1%[6] of 3-bromocyclobutene-1; a major product was 1,2-dibromocyclobutane[7] (48%[6]). This reaction is thus of doubtful value in connection with the synthesis of cyclobutadiene.

Experimental[8]

The glass liner of a 1-l. high pressure hydrogenation bomb was charged with 52.2 g. (0.293 mole) of N-bromosuccinimide (NBS), 1.14 g. (1.6 mole per cent.) of dibenzoyl peroxide and a solution of 22.8 g. (0.422 mole) of cyclobutene[9] in 211 ml. of dry C.P. benzene. The bomb was assembled, set rocking, heated to about 80° during forty-five minutes and maintained at 75–80° for seven hours; it was then allowed to cool to 4°. Working at this latter temperature to avoid losses, the contents of the bomb were washed out with 100 ml. of C.P. toluene and the suspended white crystalline solid (23.7 g., m.p. 100–119°, principally succinimide) was filtered off. Careful fractional distillation of the filtrate led to the recovery of 11.9 g. (0.22 mole) of cyclobutene. Then benzene, bromocyclobutene and some toluene were removed through a short column, collecting material of b.p. up to 48° at 100 mm.

This material, except for about 200 ml. of the most volatile part (which gave only a very weak positive test with alcoholic silver nitrate), was carefully refractionated at atmospheric pressure through a 75-cm. helix-packed heated column topped by a total reflux, variable take-off head. There was no appreciable amount of a constant-boiling bromide component. The portions (total *ca.* 12 g.) collected in the interval between benzene and toluene, which gave strong positive tests with alcoholic silver nitrate (fractions immediately before and after these gave weak tests), were treated with 20 g. of an 18% solution of trimethylamine in benzene. A cloudiness developed at once; overnight partially crystalline oil was deposited which was extracted with water; further prolonged treatment of the benzene phase with trimethylamine gave a smaller additional amount of oily salt. The aqueous extracts were evaporated to dryness *in vacuo;* total yield of crude residue 0.42 g. (1.08%[6]). To an ethanolic solution of the residue, after purification with Norit, ether was added dropwise; a colored oil precipitated and then a gummy crystalline hygroscopic solid. This latter was converted[10] to the picrate (0.30 g. = 0.43%[6]), crude m.p. 191.5–194°; recrystallization from ethanol–water gave deep-yellow, rough blades in sparse latticed clusters, m.p. 197.0–197.5°; the mixed m.p. with authentic 2-cyclobutenyltrimethylammonium picrate[11] showed no depression.

Anal. Calcd. for $C_{13}H_{16}N_4O_7$: C, 45.88; H, 4.74; N, 16.47. Found: C, 45.92; H, 4.93; N, 16.42.

On standing for four days, the residual clear brown oil (left after removing benzene and toluene from the reaction mixture) deposited 6.25 g. of massive rhombic crystals, m.p. 147–152°, identified after recrystallization as N-phenylsuccinimide[12] (mixed m.p.), yield 12.1% based on NBS. The filtrate from these crystals was distilled through a short column, first at 100 mm., then at 10 mm. A colorless oil (21.14 g.), b.p. 52.8–53.7° at 10 mm. was collected (the last portions of this fraction were removed at 3.5 mm., b.p. up to 35.3°). The oil was identified as 1,2-dibromocyclobutane[7] (48.8%[6]; 67.3% based on NBS); it solidified on cooling, melted at 3.5–4.5° and boiled at 174.5° (cor.) at 748 mm. (Émich micro method); when mixed with authentic dibromide[13] no depression of the m.p. was noted. The further distillation (from a flask with a low side arm) of the viscous material (13.2 g.) re-

(1) This study was aided by a grant from the Research Corporation.

(2) *Cf.* Buchman, Schlatter and Reims, THIS JOURNAL, **64**, 2701 (1942).

(3) Ziegler[4] recommended his method as a general tool for preparing cyclic conjugated diolefin sfrom the corresponding monoölefins. When the work reported here was already in progress, W. Baker in a Tilden Lecture (*J. Chem. Soc.*, 258 (1945)) suggested the Ziegler bromination of cyclobutene as a step in the synthesis of cyclobutadiene.

(4) *Cf.* Ziegler, *et al.*, *Ann.*, **551**, 80 (1942).

(5) Buchman and Howton, THIS JOURNAL, **70**, 2517 (1948).

(6) Based on cyclobutene consumed.

(7) See ref. 5, footnote 7.

(8) All melting points are corrected; microanalyses by Dr. G. Oppenheimer and Mr. G. A. Swinehart of this Institute.

(9) Willstätter and Bruce, *Ber.*, **40**, 3979 (1907); *cf.* Heisig, THIS JOURNAL, **63**, 1698 (1941).

(10) *Cf.* Howton, *ibid.*, **69**, 2555 (1947), footnote 5.

(11) Buchman and Howton, to be published.

(12) *Cf.* Howton, *ibid.*, **69**, 2060 (1947); *cf.* ref. 5.

(13) Prepared by bromination of cyclobutene, m. p. 4.7–5.7°, Émich b. p. 176.2° (cor.) at 741 mm.; Willstätter and von Schmaedel, *Ber.*, **38**, 1992 (1905), reported m. p. 1–4°, b. p. 171–174°.

maining after removal of the dibromide gave a 3.71 g. fraction, b.p. *ca.* 110° at 1.2 mm., which crystallized and was identified as succinimide; thus, in this experiment, essentially all of the succinimido portion of the original NBS has been accounted for as succinimide and N-phenylsuccinimide.

In another experiment, 3.0 g. of cyclobutene, 8.1 g. of NBS and 34 ml. of carbon tetrachloride were heated in a sealed tube at 75° for ninety minutes with occasional shaking; there was isolated, *inter alia*, 0.30 g. of a viscous pale brown oil, b.p. 107–109° at 1 mm. This oil contained halogen (Beilstein test), was insoluble in cold 48% hydrobromic acid and dissolved in this solvent on heating; the analysis indicated the presence of the 1:1 adduct[14] of cyclobutene and NBS.

Anal. Calcd. for $C_8H_{10}BrNO_2$: C, 41.40; H, 4.34; N, 6.04. Found: C, 40.62; H, 4.91; N, 5.84.

(14) An analogous product was obtained[5] under similar conditions from methylenecyclobutane and NBS; *cf.* ref. 5, footnote 8.

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The Synthesis of the Glycine Homolog of Thyroxine[1]

BY EARL FRIEDEN[2] AND RICHARD J. WINZLER

In a search for compounds which might prove to be competitive inhibitors of thyroxine, and to elucidate further the structural requirements for thyroxine-like activity, we have synthesized the glycine homolog of thyroxine, a compound having a glycine instead of an alanine side chain. This was accomplished, though in poor yield, by the application of a Strecker synthesis to the aldehyde, 3,5-diiodo-4-(4′-methoxyphenoxy)-benzaldehyde, prepared essentially by the method of Harington and Barger[3] and Niemann and Redemann.[4] The resulting amino acid (I) was treated with hydroiodic acid to give the 3,5-diiodo-DL-thyronine homolog (II), which was iodinated to produce 3,5-diiodo-4-(3′,5′-diiodo-4′-hydroxyphenoxy)-DL-phenylglycine. This compound has proved to be approximately one-third as active as DL-thyroxine in accelerating amphibian metamorphosis and 1/500 as active as DL-thyroxine in preventing the increase of the thyroid weights of mice fed thiouracil.[5]

Experimental

3,5-Diiodo-4-(4′-methoxyphenoxy)-DL-phenylglycine (I).—To a solution of 2.7 g. of 3,5-diiodo-4-(4′-methoxyphenoxy)-benzaldehyde in ethanol was added 15 ml. of an aqueous solution containing 1.25 g. sodium cyanide and 1.62 g. ammonium chloride. The mixture was shaken for eighteen to twenty hours at room temperature, then diluted with water and extracted with three 30-ml. portions of 6 *N* hydrochloric acid. The combined acid extracts were washed once or twice with ether. The acid solution was then heated to the boiling point for several hours while being subjected to a very gentle suction to concentrate the solution and to reduce the hydrochloric acid concentration. After filtration and cooling, a white crystalline solid, the hydrochloride of I, appeared. Neutralization of the acid mother liquor gave free I. The two fractions were dissolved in warm, dilute ammonium hydroxide, the solution filtered, and I obtained in 5–10% yield by the addition of acetic acid. I gave a positive ninhydrin reaction but a negative Folin phenol test. For elementary analysis a sample was repeatedly recrystallized as the hydrochloride from 1% hydrochloric acid. The free acid, obtained by isoelectric precipitation, was then employed for analysis. Under the microscope, it appeared as flat, rectangular crystals, m.p. 186–189°.

Anal. Calcd. for $C_{15}H_{13}O_4NI_2$ (525): C, 34.3; N, 2.7; I, 48.4. Found: C, 34.3; N, 2.8; I, 48.2.

3,5-Diiodo-4-(4′-hydroxyphenoxy)-DL-phenylglycine (II).—I, 250 mg., was dissolved in 8 ml. of glacial acetic acid and refluxed for ninety minutes with 2 ml. freshly distilled 50% hydriodic acid. The mixture was then evaporated to dryness on a water-bath, water added, and again distilled to dryness. The residue was dissolved in 15 ml. of warm dilute hydrochloric acid, filtered, and washed several times with ethyl ether. Neutralization of the aqueous fraction to *p*H 6 precipitated II in 60% yield. Since II gave a strongly positive Folin phenol test and caused an appreciable depression of melting point when mixed with an equal quantity of I, an elementary analysis was not deemed necessary. It melted at 192–194°.

3,5-Diiodo-4-(3,5′-diiodo-4′-hydroxyphenoxy)-DL-phenylglycine, (III), the Glycine Homolog of DL-Thyroxine.—When II was iodinated with iodine monochloride according to the method of Block and Powell,[6] no product could be isolated. However, iodination was effected by the method of Datta and Prosad.[7] II, 100 mg., dissolved in 3 ml. 7 *N* ammonium hydroxide, was cooled in an ice-bath, and 0.9 ml. 1 *N* potassium triiodide slowly added. The rapid decolorization of the solution indicated absorption of iodine. After allowing the mixture to stand in the cold for thirty minutes, the excess iodine was destroyed with sodium bisulfite. Neutralization of the solution with acetic acid gave crude III, as needles, in 50% yield. III was recrystallized by acidifying a dilute ammoniacal solution of the amino acid. III gave positive ninhydrin, Folin phenol tests and a red positive Kendall test for *o*-diiodophenols. III melted with decomposition at 167–170°.

Anal. Calcd. for $C_{14}H_9O_4NI_4$ (763): C, 22.0; I, 66.5; H, 1.2. Found: C, 21.7; I, 64.2; H, 1.4.

The somewhat low iodine and carbon analyses and the high hydrogen analysis can be accounted for by assuming at least partial hydration of compound III, a well known property of *o*-diiodo phenols.

(1) This work was taken from a thesis presented to the Graduate School of the University of Southern California by Earl Frieden in partial fulfillment of the requirements for the degree of Master of Science.

(2) We wish to acknowledge the support of this work by grants from the National Research Council Committee on Research in Endocrinology and from the Eli Lilly Company, and to thank the Hancock Foundation for providing laboratory facilities.

(3) C. R. Harington and G. Barger, *Biochem. J.*, **21**, 169 (1927).

(4) C. Niemann and C. E. Redemann, THIS JOURNAL, **63**, 1549 (1941).

(5) E. Frieden and R. J. Winzler, *J. Biol. Chem.*, in press.

(6) P. Block, Jr., and G. Powell, THIS JOURNAL, **64**, 1070 (1942).

(7) Datta and Prosad, *ibid.*, **39**, 441 (1917).

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A Synthesis of *cis*-1,3-Diphenyl-1-butene

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In the course of an investigation in this laboratory, it became necessary to prepare hydratroponitrile (α-phenylpropionitrile). Inasmuch as the preparative methods involving (1) the methyla-