then with water (wt. of solid 1.60 g.). The ether layer of the filtrate was extracted with two 20-ml. portions of 5% sodium bicarbonate; acidification (congo red) of the combined bicarbonate washes with sulfuric acid gave a small amount of light yellow precipitate, which was collected and washed with water.

The solution of the two above precipitates in dilute sodium carbonate was decolorized with Darco. Acidification (congo red) of the solution with sulfuric acid produced a flocculent white solid, which was collected and washed with water. Recrystallization from dioxane gave a white powdery solid (wt. 0.97 g., 40%) melting at 330–332° (lit. 339–341°,[17] 356–357°[16]) and containing no halogen.

From 3,3′-biphenyldilithium: To an ice-cold *n*-butyllithium solution in 24 ml. of dry ether, prepared from 0.56 g. of lithium and 3.4 g. of *n*-butyl chloride, contained in the apparatus described above and under an atmosphere of nitrogen, 2.34 g. of 3,3′-dibromobiphenyl in 12 ml. of dry ether was added by means of a dropping funnel over a thirty-minute period. The mixture was cooled and stirred for four hours and was then gently refluxed for one hour. After carbonation of the mixture, the acid was isolated and purified as above, m. p. 330.5–332° (wt. 0.83 g., 46%).

Dimethyl Ester of 3,3′-Biphenyldicarboxylic Acid.—The procedure of Bulow and von Reden[17] was employed. The dimethyl ester so obtained melted at 97.5–99 (lit.[17] 100–101).

3′-Bromo-3-biphenylcarboxylic Acid.—To 3.20 g. of 3,3′-dibromobiphenyl, 0.24 g. of magnesium and 20 ml. of dry ether, contained in the apparatus previously described and under an atmosphere of nitrogen, approximately 0.005 mole of ethylmagnesium bromide in 5 ml. of dry ether was added; the mixture was stirred and gently heated for seven hours. The reaction mixture was carbonated and hydrolyzed as before.

From the hydrolysis mixture, 0.31 g. of light yellow solid (m. p. above 300°) was removed by filtration and washed with several small portions of ether. The separated ether layer was extracted with two 20-ml. portions of 5% sodium bicarbonate, then with two 20-ml. portions of 5% sodium hydroxide.

The combined sodium bicarbonate washes were decolorized with Darco, and acetic acid was added until the solution was almost neutral to litmus. A precipitate (A, wt. 0.59 g.) was collected and washed with water. Acidification (congo red) of the filtrate from A with sulfuric acid gave a second precipitate (B, wt. 0.13 g.). Similar treatment of the sodium hydroxide extracts with acetic acid gave a precipitate (C, wt. 0.37 g.); on further acidification of the filtrate no appreciable precipitate was obtained.

A portion of C was dissolved in dilute sodium carbonate and decolorized with Darco. Acidification of the filtered solution gave a white solid which was removed by filtration, washed with water and dried. The solid, which contained bromine, was recrystallized twice from benzene to give 3′-bromo-3-biphenylcarboxylic acid, melting at 190–191°.

Anal. Calcd. for $C_{13}H_9O_2Br$: C, 56.34; H, 3.27. Found: C, 56.76; H, 3.54.

Precipitate A consisted primarily of the monobasic acid as shown by its almost complete liquefaction at a temperature of 190° and by its separation into the mono- and dibasic acids by stepwise acidification of its solution in dilute sodium carbonate. Precipitate B was primarily the dibasic acid as shown by the melting point, roughly determined as above 300°.

Summary

3,3′-Dibromobiphenyl has been synthesized from *o*-nitrobromobenzene by zinc–alkali reduction to 2,2′-dibromohydrazobenzene, rearrangement of the hydrazo compound to 3,3′-dibromobenzidine, and deamination of the benzidine by reaction of the tetrazonium salt with hypophosphorous acid. A dilithium compound and a difunctional Grignard reagent were prepared from 3,3′-dibromobiphenyl. From the monofunctional Grignard reagent the new 3′-bromo-3-biphenylcarboxylic acid was obtained.

The melting points of the 2,2′-dibromohydrazobenzene and 3,3′-dibromobenzidine prepared in this work do not agree with those of substances previously considered to have these structures.

URBANA, ILLINOIS RECEIVED JULY 26, 1948

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

The Stereochemical Course of Amine Replacement Reactions. Some Reactions of *d*-(+)-N,N,N-Trimethyl-α-phenylethylammonium Iodide

BY H. R. SNYDER AND JAMES H. BREWSTER[1]

Quaternary ammonium compounds containing benzyl groups can be used in the benzylation of the anions of such salts as sodiomalonic ester,[2] sodium cyanide,[3] sodium phenolate,[3,4] and the sodium salts of carboxylic acids[3] or of sulfur containing acids.[3,5] These reactions appear to be completely analogous to the formation of benzyl alcohol[6] and benzyl chloride[7] by thermal decomposition of quaternary benzylammonium hydroxides and chlorides, and it would be expected that all of these processes occur by similar mechanisms.

Evidence has been presented to show that both methanol and benzyl alcohol are formed from benzyltrimethylammonium hydroxide by reactions having S_N2 mechanisms.[8,9] Reactions proceeding by such mechanisms occur with complete inversion of configuration when they take place at an asymmetric carbon atom; other mechanisms result in partial or complete racemization or in retention of configuration.[10] Read and

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[1] Present address: Department of Chemistry, University of Chicago, Chicago, Illinois.

[2] Snyder, Smith and Stewart, THIS JOURNAL, **66**, 200 (1944).

[3] von Meyer, *Abhandl. math.-phys. Klasse sachs. Gesellschaft Wiss.*, **31**, 179 (1908); [*Chem. Zentr.*, **80**, II, 1800 (1909)].

[4] Hla Baw, *Quart. J. Indian Chem. Soc.*, **3**, 101 (1926); [*C. A.*, **20**, 3695 (1926)].

[5] Snyder and Speck, THIS JOURNAL, **61**, 668, 2895 (1939).

[6] von Braun, *Ann.*, **382**, 1 (1911).

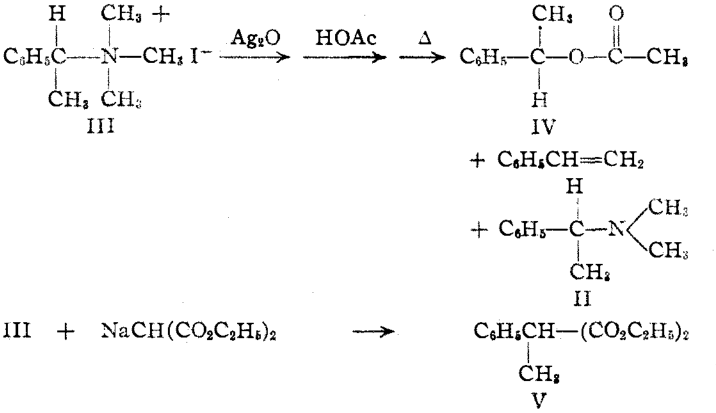
[7] Michler and Gradmann, *Ber.*, **10**, 2078 (1877).

[8] Hughes and Ingold, *J. Chem. Soc.*, 69 (1933).

[9] Hughes, Ingold and Patel, *ibid.*, 526 (1933).

[10] Cowdrey, Hughes, Ingold, Masterman and Scott, *ibid.*, 1252 (1937).

Walker[11] concluded that Walden inversion occurred in the formation of *d*-neopiperitol from *l*-piperityltrimethylammonium hydroxide. Accordingly it would be anticipated that an optically active quaternary salt containing an α-substituted benzyl group would alkylate the various reagents mentioned above to give products of configuration opposite to that of the original salt. The present work was undertaken to test this assumption. Optically active forms of α-phenylethyltrimethylammonium salts were chosen for the experiments because the configurational relationships of a large number of compounds containing the α-phenylethyl group have been established.[12] These relationships may be summarized in the statement that in the α-phenylethyl series optically active halo, hydroxy, amino, dimethylamino and acetoxy compounds which have the same sign of rotation have the same configuration.



$$C_6H_5CH(CH_3)N^+(CH_3)_3\,I^- \text{ (III)} \xrightarrow{Ag_2O} \xrightarrow{HOAc} \xrightarrow{\Delta} C_6H_5CH(CH_3)OCOCH_3 \text{ (IV)} + C_6H_5CH{=}CH_2 + C_6H_5CH(CH_3)N(CH_3)_2 \text{ (II)}$$

$$\text{III} + NaCH(CO_2C_2H_5)_2 \longrightarrow C_6H_5CH(CH_3){-}(CO_2C_2H_5)_2 \text{ (V)}$$

α-Phenylethylamine (I) was resolved by means of malic and tartaric acids.[13] The optical purity of the *d*-(+)-form ($[\alpha]^{25}_{D}$ +36.24°, $[\alpha]^{22}_{D}$ +36.60°) was estimated to be no more than 97.5%, on the basis of the rotation observed by Marckwald and Meth[14] ($[\alpha]^{22}_{D}$ 37.70°), and to be no less than 94.5%, on the basis of the rotation found by Holmberg[15] ($[\alpha]^{19}_{D}$ 38.73°). The optically active primary amine was methylated by means of formaldehyde and formic acid. N,N-Dimethyl-α-phenylethylamine (II) has a high rotation ($[\alpha]^{26}_{D}$ +61.76°) and might be a useful resolving agent; it forms a methiodide (III) which is dextrorotatory in water.

A water solution of the methiodide (III) was treated with silver oxide and then with acetic acid; the solution of the quaternary acetate was distilled to dryness. From the distillate there was obtained 1-(−)-α-phenylethyl acetate (IV) (26.3%) ($[M]^{28}_{D}$ −185.1 in benzene) having an estimated optical purity of 95.4%, based on the value of Levene and Marker[16] ($[M]^{25}_{D}$ −194 in benzene). Thus, inversion of configuration occurred to the extent of 98–100%, strongly indicating an S_N2 mechanism for the reaction. Styrene (33.1%) and *d*-(+)-II (12.1%) were also obtained from this degradation.

Sodiomalonic ester can be alkylated by the racemic salt (III) in diethyl carbitol solution. When the optically active methiodide was employed, the α-methylbenzylmalonic ester (V) formed was optically inactive. A small amount of weakly dextrorotatory II was also obtained, suggesting that the quaternary salt was largely racemized before it could participate in the alkylation reaction.

When an aqueous solution of III and sodium cyanide was distilled to dryness none of the desired hydratroponitrile could be isolated from the distillate, which appeared to consist mainly of styrene.

Experimental

***d*-(+)-α-Phenylethylamine (I).**—*dl*-α-Phenylethylamine (60 g., 0.50 mole) was resolved by the successive use of *l*-malic acid and *d*-tartaric acid[13] to give 16.1 g. (53.7%) of *d*-(+)-α-phenylethylamine, n^{20}_{D} 1.5264; d^{20}_{4} 0.951; $[\alpha]^{25}_{D}$ +36.24°, $[\alpha]^{22}_{D}$ +36.60° (l = 1 dcm.).

***dl*- and *d*-(+)-N,N-Dimethyl-α-phenylethylamine[17] (II).**—The general method of "Organic Syntheses"[18] for the methylation of amines was found to be applicable to α-phenylethylamine. *dl*-N,N-Dimethyl-α-phenylethylamine, b. p. 92–94° (30 mm.), n^{20}_{D} 1.5023, d^{20}_{4} 0.908 (lit.[12c] n^{14}_{D} 1.5025, d^{16}_{4} 0.8986), was obtained in 75% yield, and *d*-(+)-N,N-dimethyl-α-phenylethylamine, n^{20}_{D} 1.5025, d^{20}_{4} 0.908. $[\alpha]^{26}_{D}$ +61.76° (l = 1 dcm.), in 64.5% yield.

***dl*- and *d*-(+)-N,N,N-Trimethyl-α-phenylethylammonium Iodide (III).**—To a solution of N,N-dimethyl-α-phenylethylamine (60.0 g., 0.40 mole) in ether (100 ml.) was added slowly a solution of methyl iodide (64.0 g., 0.45 mole) in ether (100 ml.). After fifteen minutes the mixture had solidified. The flask was cooled under the tap several times during the succeeding two hours and then let stand at room temperature for fourteen hours. The white solid was collected by filtration and washed with two 100-ml. portions of ether. After it had been dried in the air and finally in a vacuum desiccator (continuous pumping for twenty-four hours) the solid weighed 111 g. (95%).

In a similar manner, *d*-(+)-α-phenylethylamine (9.5 g., 0.064 mole) was converted to its methiodide, 17.0 g. (92%), m. p. 157° $[\alpha]^{26}_{D}$ + 11.88 (in water) (c = 1.2627) [lit.[19] m. p. 157.0–157.5°, $[\alpha]^{26}_{D}$ + 19.60° (in alcohol) (c = 2.5)].

Degradation of *d*-(+)-N,N,N-Trimethyl-α-phenylethylammonium Acetate.—The still moist, thoroughly washed silver oxide prepared from 11.0 g. of silver nitrate

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(11) Read and Walker, *J. Chem. Soc.*, 308 (1934).

(12) (a) Levene, Rothen and Kuna, *J. Biol. Chem.*, **120**, 777 (1937); (b) Levene and Rothen, *ibid.*, **127**, 237 (1939); (c) Campbell, Houston and Kenyon, *J. Chem. Soc.*, 93 (1947); (d) Bergmann, *Helv. Chim. Acta.*, **20**, 590 (1937); (e) Hughes, Ingold and Scott, *J. Chem. Soc.*, 1201 (1937); (f) Ott, Zinnius, Wegler, Beischer and Packendorf, *Ann.*, **488**, 186 (1931); (g) Wegler and Ruber, *Ber.*, **68**, 1055 (1935).

(13) Ingersoll, in "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1943, p. 506.

(14) Marckwald and Meth, *Ber.*, **38** 808 (1905).

(15) Holmberg, *ibid.*, **45**, 999 (1912).

(16) Levene and Marker, *J. Biol. Chem.*, **97**, 379 (1932).

(17) Stevens, *J. Chem. Soc.*, **2107** (1930).

(18) Icke, Wisegarver and Alles, "Organic Syntheses," Vol. XXV, John Wiley and Sons, Inc., New York, N. Y., 1945, p. 89.

(19) Billmann, Jensen and Jensen, *Bull. soc. chim.*, [5] **3**, 2295 (1936).

was added slowly, and with good stirring, to a warm (50°) solution of *d*-(+)N,N,N-trimethyl-α-phenylethylammonium iodide (11.64 g., 0.04 mole) in water (100 ml.). The precipitate of silver iodide was broken up continuously to expose fresh silver oxide until the precipitate as a whole was light brown in color. The silver oxide–silver iodide precipitate was removed by filtration and washed with four 50-ml. portions of water. The combined filtrate and wash water was treated with glacial acetic acid (30 g., 0.50 mole), and concentrated to a thick sirup on a steam cone at the water pump.

This oil was transferred, while still warm, to a 50-ml. distilling flask with a wide low-set side arm. Two 1-ml. portions of water and two 1-ml. portions of glacial acetic acid were used in this transfer. The solution in the distilling flask was then distilled at 34 mm. pressure with a Woods metal-bath to heat the bulb of the flask. Most of the excess water and[5] acetic acid distilled below 80° (bath temperature 130° or less). When the bath temperature reached 170–175°, vigorous ebullition occurred and the entire contents of the flask distilled smoothly and rapidly (vapor temperature, 80–110°). The distillate had a strong odor of acetic acid, and weighed 9.5 g.

The distillate was dissolved in ether (50 ml.) and extracted with three 50-ml. portions of water and then with two 25-ml. portions of 5% aqueous sodium bicarbonate. The five aqueous washings were combined (A).

The ether solution was distilled at atmospheric pressure and then at water pump pressure. Fractions which distilled at 69–71° (30 mm.) and at 118–119° (30 mm.) were collected.

The lower-boiling fraction, identified as styrene, weighed 1.38 g. (33.1%); n^{20}_{D} 1.5455, dibromide, m. p. 73–74° (lit., b. p. 145–145.8°[20] (n^{20}_{D} 1.5463,[20] dibromide m. p. 74–75°).[21]

The higher-boiling fraction was 1-(−)-α-phenylethyl acetate; it weighed 1.72 g. (26.3%); n^{20}_{D} 1.4953 (after two further distillations); $[\alpha]^{28}_{\mathrm{D}}$ −112.9° (in benzene) (c = 0.1196); $[\alpha]^{28}_{\mathrm{D}}$ −112° (homogeneous) (l = 1 dcm.) (capillary); $[M]^{28}_{\mathrm{D}}$ −185.1° (lit., b. p. 104° (23 mm.),[12d] n^{20}_{D} 1.49432,[22] ($[M]^{25}_{\mathrm{D}}$ −194°).[16]

To the combined aqueous extracts (A) was added 15 ml. of 37% hydrochloric acid. The solution was then evaporated to dryness on a steam cone at the water pump. The white solid was taken up in four 3-ml. portions of water, and these solutions were combined and treated with a solution of sodium hydroxide (10 g.) in water (15 ml.). A vigorous evolution of a basic gas, probably trimethylamine, occurred and an organic liquid separated. The aqueous mixture was extracted three times with 10-ml. portions of ether. The ether was distilled at atmospheric pressure, and the residue was distilled at 31 mm. to yield *d*-(+)-N,N-dimethyl-α-phenylethylamine, b. p. 95–96° (31 mm.), 0.72 g. (12.1%), n^{20}_{D} 1.5021, $[\alpha]^{27}_{\mathrm{D}}$ + 59.04 (homog.) (l = 1 dcm.).

Alkylation of Malonic Ester with *d*-(+)-N,N,N-Trimethyl-α-phenylethylammonium Iodide.—It was found that absolute diethyl carbitol[23] is a superior solvent for the alkylation of sodiomalonic ester with quaternary salts containing the α-phenylethyl group, for styrene formation was much lower in non-protonic solvents than in the more acidic solvents, such as alcohol. Diethyl carbitol is a polyfunctional ether, and as such has greater solvent powers than dibutyl ether.

Sodium (0.51 g., 0.022 mole) was converted to sodium sand in dry xylene. This operation was carried out in a 50-ml. round-bottomed flask with a ground joint and a gas-inlet side-arm. The xylene was decanted from the sodium sand, and was immediately replaced by about 15 ml. of absolute diethyl carbitol. This was in turn decanted from the sodium, and fresh absolute diethyl carbitol (25 ml.) was added at once. The flask was then fitted with a two-necked adapter bearing a reflux condenser and a small Hershberg stirrer. Diethyl malonate (8.0 g., 0.05 mole) was added slowly to the well-cooled, stirred suspension of sodium sand. After the initial vigorous reaction had subsided and most of the sodium had gone into solution, the cooling-bath was removed, and the reaction allowed to proceed at room temperature. Sodiomalonic ester is quite soluble in diethyl carbitol and the reaction was complete within an hour. Powdered dry *d*-(+)-N,N,N-trimethyl-α-phenylethylammonium iodide (8.73 g., 0.03 mole) was added rapidly. A source of nitrogen was attached to the gas-inlet side-arm of the flask, and the system was flushed out with nitrogen.

The flask was heated by means of an oil-bath. While the contents of the flask were vigorously stirred the oil-bath was maintained at a temperature of 130–140° for twenty-four hours. The temperature of the bath was raised to 150° and held there for one-half hour. During all of this heating only a slow evolution of trimethylamine was noted.

To the cooled mixture in the flask was added 10% hydrochloric acid (20 ml.) and benzene (25 ml.). The organic layer was separated from the acidic aqueous layer.

The benzene solution was extracted with two 50-ml. portions of 5% sodium bicarbonate solution and then with three 25-ml. portions of 37% hydrochloric acid. Diethyl carbitol is wholly extracted from the benzene by this procedure. The benzene solution was distilled, finally under reduced pressure. The fraction boiling at 118–120° (1 mm.) was collected; it consisted of α-methylbenzylmalonic ester (V) 0.93 g. (17.5%), n^{20} 1.4752. This material was optically inactive.

The substituted malonic ester was saponified by the use of 50% potassium hydroxide. The malonic acid so formed melted at 144–145°.[24]

The aqueous solution obtained when hydrochloric acid was added to the reaction mixture was made strongly basic by the addition of 10% sodium hydroxide. The liquid which separated was taken up in ether. The ether solution was evaporated and the residue was distilled. The fraction boiling at 95–96° (30 mm.) was collected; weight 0.72 g. (24.2%), n^{20}_{D} 1.5003, $[\alpha]^{27}_{\mathrm{D}}$ + 19.06 (homog.) (l = 1 dcm.). The material was largely racemized N,N-dimethyl-α-phenylethylamine.

Summary

1(−)-α-Phenylethyl acetate has been prepared from *d*-(+)-N,N,N-trimethyl-α-phenylethylammonium iodide by amine replacement. Essentially complete Walden inversion occurred, indicating an S_N2 mechanism for the replacement reaction.

Although the quaternary salt can be used in the alkylation of malonic ester, extensive racemization occurs during the long heating period required.

URBANA, ILLINOIS RECEIVED JULY 30, 1948

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(24) Fischer and Schmitz, *Ber.*, **39**, 353, 2210 (1906).