9-β-D-Glucopyranosylisoguanine.—A solution of 0.40 g. of 2,6-diamino-9-β-D-glucopyranosylpurine and 0.50 g. of sodium nitrite in 7 ml. of hot water was cooled to 50° and treated with 0.50 ml. of glacial acetic acid. The mixture was kept at 50° for five minutes, and the resulting clear brown solution diluted with 25 ml. of water. A solution of 1.50 g. of lead acetate trihydrate in 15 ml. of water was added, followed by 6 ml. of concentrated aqueous ammonia. The precipitate was collected by centrifugation, washed, and dissolved in 30 ml. of 20% acetic acid. The solution was treated with hydrogen sulfide, filtered, and the filtrate evaporated to dryness. Crystallization of the residue from 10 ml. of water, with Norit, gave 0.19 g. of small leaflets; a further 0.03 g. was obtained by concentration of the mother liquors; total yield 0.22 g. (55%). Recrystallization from water gave 0.15 g. of tiny colorless leaflets, m.p. 279–282° (dec.), with previous darkening above 270° (reported,[9] m.p. 265–270° (dec.)); $[\alpha]^{24}D$ −26° (*c* 1.01% in 0.1 *N* sodium hydroxide). On a paper chromatogram in a *n*-butanol–diethylene glycol–water mixture in an ammonia atmosphere,[11] the R_f value was 0.15.

Anal. Calcd. for $C_{11}H_{15}O_6N_5$: C, 42.16; H, 4.79; N, 22.35. Found: C, 42.00; H, 4.83; N, 22.45.

Crotonoside (Natural).—This was prepared from croton beans as described by Falconer, *et al.*,[5] and was purified by conversion to the picrate and regeneration by the use of an anion-exchange resin.[8] It formed needles and needle clusters, m.p. between 237 and 252° (dec.), depending on the rate of heating; $[\alpha]^{26}D$ −71° (*c* 1.06% in 0.1 *N* sodium hydroxide). The ultraviolet absorption spectra, at *c* = 22.9 mg. per liter, showed maxima as follows: In water, 247 mμ (ϵ_m 8,930) and 293 mμ (ϵ_m 11,100); in 0.05 *N* hydrochloric acid, 235 mμ (ϵ_m 6,140) and 283 mμ (ϵ_m 12,700); and in 0.05 *N* sodium hydroxide, 251 mμ (ϵ_m 6,890) and 285 mμ (ϵ_m 10,550). [Falconer, *et al.*,[5] gave the following maxima: In water, 235 mμ (ϵ_m 8,600) and 284 mμ (ϵ_m 9,100); in 0.05 *N* hydrochloric acid, 270 mμ (ϵ_m 10,500); and in 0.05 *N* sodium hydroxide, 240 mμ (ϵ_m 4,000) and 275 mμ (ϵ_m 7,400)]. On paper chromatography as described for the glucosylpurine, the compound gave one spot, R_f value 0.23.

Anal. Calcd. for $C_{10}H_{13}O_5N_5$: C, 42.40; H, 4.63; N, 24.73. Found: C, 42.45; H, 4.96; N, 24.72.

Picrate.—Prepared in aqueous solution and recrystallized from water, the picrate formed needles, decomposing at 212–225°.

9-β-D-Ribofuranosylisoguanine.—A solution of 0.30 g. of 2,6-diamino-9-β-D-ribofuranosylpurine and 0.45 g. of sodium nitrite in 5 ml. of hot water was cooled to 50° and treated with 0.45 ml. of glacial acetic acid. The resultant gelatinous mass was kept at 50° for five minutes, then diluted with 15 ml. of water, heated to give a clear solution, and the compound isolated through the lead salt exactly as described for the corresponding glucosylpurine; yield 0.172 g. (57%). The material was twice recrystallized from water, with Norit, to give 0.12 g. of minute needles and needle clusters. The compound had the same melting point as crotonoside at any given rate of heating; mixtures with crotonoside melted one to two degrees lower; $[\alpha]^{26}D$ −72.5° (*c* 0.73% in 0.1 *N* sodium hydroxide). The ultraviolet absorption spectra in water, 0.05 *N* hydrochloric acid and 0.05 *N* sodium hydroxide were indistinguishable from those of crotonoside under similar conditions. On paper chromatography as described for the glucosylpurine the compound gave one spot, R_f value 0.23.

Anal. Calcd. for $C_{10}H_{13}O_5N_5$: C, 42.40; H, 4.63; N, 24.73. Found: C, 42.38; H, 4.55; N, 24.96.

Prepared in aqueous solution and recrystallized from water, the **picrate** formed needles, decomposing at 210–225° alone or in admixture with crotonoside picrate.

Hydrolysis of the synthetic ribosylisoguanine with *N* hydrochloric acid for one hour at 100° gave isoguanine, identified by its ultraviolet absorption spectrum[12] and by paper chromatography.

Acknowledgment.—The author wishes to thank Dr. A. Bendich, of this Laboratory, for a sample of natural crotonoside; Dr. Carl Clark, of Cornell University Medical College, for determining the X-ray diffraction patterns and infrared absorption spectra of specimens of crotonoside; Mr. Roscoe C. Funk, Jr., for the microanalyses; and Dr. George Bosworth Brown for his interest in this work.

(11) E. Vischer and E. Chargaff, *J. Biol. Chem.*, **176**, 703 (1948).

(12) A. Bendich, J. F. Tinker and G. B. Brown, THIS JOURNAL, **70**, 3109 (1948).

NEW YORK, N. Y. RECEIVED JANUARY 26, 1951

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, MASSACHUSETTS INSTITUTE OF TECHNOLOGY]

Small-Ring Compounds. VI. Cyclopropanol, Cyclopropyl Bromide and Cyclopropylamine

BY JOHN D. ROBERTS AND VAUGHAN C. CHAMBERS

Assignment by Cottle and co-workers of the cyclopropanol structure to one of the products of the reaction of ethylmagnesium bromide with epichlorohydrin has been verified by an independent synthesis from cyclopropylmagnesium chloride. Cyclopropyl acetate and *p*-toluenesulfonate have been prepared and characterized. Cyclopropyl bromide has been obtained from the reaction of silver cyclopropanecarboxylate with bromine. The von Braun reaction between N-cyclopropylbenzamide and phosphorus pentabromide was unsuccessful. The Beckmann rearrangement of cyclopropyl methyl ketoxime has been investigated as part of a synthesis of cyclopropylamine.

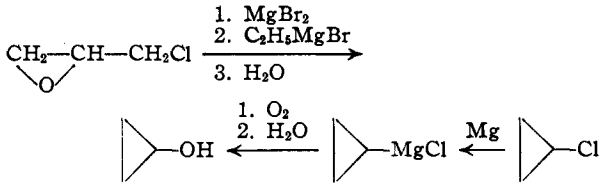
Cyclopropanol (I) has been reported by Cottle and co-workers[1] to be formed in the reaction of ethylmagnesium bromide with epichlorohydrin. Although the alcohol was not obtained pure, a large number of solid derivatives were prepared having the correct elemental analyses. The cyclopropanol structure was assigned indirectly on the basis of the non-identity of the compound and its derivatives with the known three-carbon alcohols as well as the rather facile formation of propionaldehyde on heating.[2]

In the present investigation, the preparation of I by the previously described method[1] has been duplicated and somewhat purer (halogen-free) product obtained by a slight modification of the isolation procedure. Analytically pure cyclopropanol was not obtained and, in agreement with earlier observations,[1] the material rearranged rather easily to propionaldehyde. The assignment of the cyclopropanol structure was verified by

(1) (a) J. K. Magrane and D. L. Cottle, THIS JOURNAL, **64**, 484 (1942); (b) G. W. Stahl and D. L. Cottle, *ibid.*, **65**, 1782 (1943).

(2) The work of Cottle and co-workers[1] seems to have been rather generally overlooked and the preparation and properties of cyclopropanol are not mentioned in recent books or reviews such as: P. Karrer, "Organic Chemistry," 4th English ed., Elsevier Publishing Company, Inc., New York, N. Y., 1950; G. M. Dyson, "A Manual of Organic Chemistry for Advanced Students," Vol. I, Longmans Green and Co., New York, N. Y., 1950; L. I. Smith, "Record of Chemical Progress," Kresge-Hooker Scientific Library, Detroit, Mich., Spring 1950 issue, p. 71.

synthesis in small yield of a material (II) through oxidation of cyclopropylmagnesium chloride. Solid derivatives prepared from I and II were identical.



The cyclopropylmagnesium chloride was prepared from cyclopropyl chloride obtained from the chlorination of cyclopropane.[3] The rate of reaction of cyclopropyl chloride with magnesium in diethyl ether was quite slow and was incomplete even after several days at the reflux temperature. The formation of a cyclopropyl Grignard reagent in the reaction was substantiated by treatment with phenyl isocyanate which gave cyclopropanecarboxanilide. No previous examples of the preparation and use of cyclopropylorganometallic compounds have been found in the literature.

Magrane and Cottle[1a] were unsuccessful in an attempt to prepare pure cyclopropyl acetate by the reaction of cyclopropanol (I) with acetyl chloride. It has now been shown that the ester can be prepared in fair yields from I and acetyl chloride or acetic anhydride in pyridine. Cyclopropyl *p*-toluenesulfonate was prepared similarly from I and *p*-toluenesulfonyl chloride in 86% yield. The *p*-toluenesulfonate is quite unreactive and with alcoholic 1 *N* sodium hydroxide at the reflux temperature the ester was only a few per cent. reacted after several hours.[4] Under similar conditions, *n*-propyl *p*-toluenesulfonate was completely saponified in less than two hours.

The extremely low chemical reactivity and concomitant limited synthetic usefulness of cyclopropyl chloride[4,5] have prompted an investigation of possible syntheses for cyclopropyl bromide. The von Braun reaction between N-cyclopropylbenzamide and phosphorus pentabromide was unsuccessful. Under mild conditions, the amide was recovered unchanged and, in more drastic circumstances, extensive decomposition occurred. The successful preparation of cyclobutyl bromide[6] by the Hunsdiecker reaction suggested the possibility of a similar synthesis of cyclopropyl bromide, although the expected b.p. of the product (~70°) appeared to preclude the use of carbon tetrachloride as a reaction solvent. Fair yields (15–20%) of impure cyclopropyl bromide were obtained from the reaction of bromine with silver cyclopropanecarboxylate using *sym*-tetrachloroethane as solvent. Better results (52–62% yields of pure cyclopropyl bromide) were achieved with dichlorodifluoromethane (b.p. −30°) as the reaction medium and the use of this substance appears to be particularly advantageous when a low reaction temperature is desired. The structure of the cyclopropyl bromide was indicated by the elemental analysis and lack of reaction with aqueous potassium permanganate or silver nitrate solution. The bromide readily formed a Grignard reagent and the latter was converted to cyclopropanecarboxanilide on treatment with phenyl isocyanate.

Need of substantial quantities of cyclopropylamine in this and other investigations has led to a study of a synthesis *via* the Beckmann rearrangement of cyclopropyl methyl ketoxime. Rearrangement of the oxime with phosphorus pentachloride in ether in the conventional manner gave 20–35% yields of a mixture of N-methylcyclopropanecarboxamide and N-cyclopropylacetamide. A number of other rearrangement catalysts such as acetic acid, phosphoric acid and sulfuric acid were ineffective, either giving no reaction or much decomposition. The most satisfactory procedures involved formation and rearrangement of the benzenesulfonate of the ketoxime. In the early preparations, the crude benzenesulfonate (from the reaction of the oxime with benzenesulfonyl chloride and pyridine in ether) was solvolyzed in small batches in acetic acid–water solution. However, since the solvolysis reaction was quite violent and the benzenesulfonate dangerous to handle, this method was discarded in favor of a process where the benzenesulfonate was made and solvolyzed as fast as it was formed in hot dioxane–water solution. With this procedure, yields as high as 80% of mixed amides were obtained in 2.5-mole runs. On alkaline hydrolysis, the product from the benzenesulfonate reaction in dioxane–water gave 85% of cyclopropylamine and, with the benzenesulfonate procedure, the over-all yield (three steps) of cyclopropylamine from cyclopropyl methyl ketone was 68%.

Experimental

Cyclopropanol. A. From Epichlorohydrin.—The procedure was essentially that of Stahl and Cottle[1b] except that the reaction mixture was hydrolyzed by pouring into iced ammonium chloride solution. The ether layer was separated and extracted with eight 100-ml. portions of water. The aqueous layer and extracts were combined, saturated with sodium chloride and extracted continuously with ether for two days. The ether extract was dried for four hours over calcium sulfate and then fractionally distilled through a 30 cm. Vigreux column. The yield of crude cyclopropanol from 38 g. (0.30 mole) of epichlorohydrin was 8.1 g. (46%); b.p. 53–55° (100 mm.), $n^{25}D$ 1.4108–1.4120, d^{25}_4 0.917. All of the fractions gave positive fuchsin aldehyde tests. Halogens were not present (sodium fusion) but the material did not have a satisfactory analysis.

Anal. Calcd. for C_3H_6O: C, 62.03; H, 10.41. Found: C, 60.68; H, 10.15.

The N-phenylcarbamate and N-α-naphthylcarbamates had m.p. 100.8–101.5° (lit.[1b] 101.5–102°) and 103.6–104.4° (lit.[1b] 100.5–101.5°) after recrystallization from cyclohexane.

B. **From Cyclopropylmagnesium Chloride.**—A mixture of 15 g. (0.2 mole) of cyclopropyl chloride,[3] 4.8 g. (0.2 g. atom) of magnesium, several crystals of iodine and 75 ml. of anhydrous ether was stirred and refluxed in an all-glass apparatus under a nitrogen atmosphere for three days. The resulting thick white mixture, which contained excess magnesium, was cooled in an ice-bath and dry oxygen gas bubbled through for three hours. The Grignard complexes were decomposed with iced ammonium chloride solution and the organic products extracted with ether. The ether extracts were dried over magnesium sulfate and the ether distilled. The dark residue (5 ml.) was distilled at atmospheric pressure and yielded 1 g. (9%) of crude cyclopropanol, b.p. 95–105°. The N-phenyl and N-α-naphthylcarbamates prepared from this material did not depress the

(3) J. D. Roberts and P. H. Dirstine, THIS JOURNAL, **67**, 1281 (1945).

(4) More detailed information concerning kinetics and mechanisms of the reactions of cyclopropyl *p*-toluenesulfonate (as well as other cyclopropyl derivatives) will be presented in a later paper.

(5) G. Gustavson, *J. prakt. Chem.*, [2] **43**, 396 (1891).

(6) J. Cason and R. L. Way, *J. Org. Chem.*, **14**, 31 (1949).

m.p.'s of the corresponding derivatives of the product of the epichlorohydrin reaction.

The structure of the cyclopropylmagnesium chloride was established by reaction with phenyl isocyanate. The product so obtained had m.p. 108–109° after two recrystallizations from benzene–hexane and did not depress the m.p. of an authentic sample of cyclopropanecarboxanilide, m.p. 111–112°, prepared by the reaction of the acid chloride with aniline.

Cyclopropyl Acetate.—Acetyl chloride (6.5 g., 0.08 mole) was added dropwise over one hour to a stirred ice-cooled solution of 4 g. (0.07 mole) of cyclopropanol in 11 g. (0.14 mole) of dry pyridine. After two hours, the mixture was poured into ice-water and extracted with ether. The ether extract was washed with 5% sodium bicarbonate, water, 5% hydrochloric acid, 5% sodium bicarbonate and water. It was then dried over potassium carbonate and distilled. The yield of crude cyclopropyl acetate, b.p. 108–111°, $n^{25}D$ 1.4008–1.4065 was 2.3 g. (33%).

The product was combined with 2.8 g. of a similar material, b.p. 111–112° (obtained from the reaction of 3.5 g. (0.016 mole) of cyclopropanol with a mixture of 8 g. (0.08 mole) of acetic anhydride and 1 g. of pyridine) and distilled through an efficient center-tube column.[7] The pure ester, b.p. 111.8°, had $n^{25}D$ 1.4058–1.4059 and d^{25}_4 0.9724.

Anal. Calcd. for $C_5H_8O_2$: C, 59.98; H, 8.06. Found: C, 60.06; H, 7.98.

Cyclopropyl *p*-Toluenesulfonate.—The procedure was similar to that used by Sekera and Marvel[8] for the preparation of *p*-toluenesulfonates of low molecular weight alcohols. The ester was purified by shaking with aqueous sodium hydroxide to remove unreacted *p*-toluenesulfonyl chloride. Distillation of the crude product from 5.7 g. (0.098 mole) of cyclopropanol in a molecular still at 110–120° (0.1–0.5 mm.) yielded 18.1 g. (86%) of cyclopropyl *p*-toluenesulfonate; $n^{25}D$ 1.5209, d^{25}_4 1.2045. The ester was only about 15% hydrolyzed in refluxing alcoholic 1 *N* sodium hydroxide solution after several hours.

Anal. Calcd. for $C_{10}H_{12}O_3S$: C, 56.57; H, 5.70; S, 15.10. Found: C, 56.83; H, 6.07; S, 14.84.

Cyclopropyl Bromide.—Cyclopropanecarboxylic acid (25 g., 0.29 mole), was neutralized with cold 30% ammonium hydroxide. A solution of 50 g. (0.29 mole) of silver nitrate in 100 ml. of water was added slowly with stirring. Additional water was added as the mixture became thick and finally, at the completion of the addition, the total volume of water was about 1.5 l. The silver salt was dissolved by heating and it crystallized on standing in white needles. The solid was collected, the filtrate concentrated and further crops obtained. After four concentrations, the yield of silver cyclopropanecarboxylate, dried in a steam oven overnight, was 52.5 g. (95%). The material was further dried overnight at 0.5 mm. at 100° before use.

Into a dry 1-l. three-necked flask fitted with stirrer, Dry-Ice reflux condenser, and a solid-addition tube was condensed 400 ml. of commercial dichlorodifluoromethane (Freon) dried by passage through a phosphorus pentoxide tower. After the addition of 20 g. (0.125 mole) of bromine, 24 g. (0.125 mole) of dry silver cyclopropanecarboxylate was added in small portions with vigorous stirring over a period of one hour. The bromine color faded, and when the equivalent amount of silver salt was added, the solution became tan in color. The mixture was stirred for three to five hours and the dichlorodifluoromethane distilled through a 40-cm. Vigreux column. After the solvent was gone, bromine began to reappear in the reaction mixture and the flask was packed at once in ice and the ice allowed to melt overnight. A small-scale run exploded mildly when the flask was brought to room temperature directly after removal of the solvent. The volatile products were distilled into a Dry-Ice cooled receiver at 5 mm. Some bromine was present in the distillate and was removed by the addition of several drops of amylene. The resulting mixture was distilled through a 10-cm. Vigreux column and yielded 7.9 g. (53%) of cyclopropyl bromide, b.p. 68–69.7°. The products of two such runs were combined and fractionated through an efficient column.[7] The pure cyclopropyl bromide so obtained had b.p. 69°, $n^{25}D$ 1.4572, d^{25}_4 1.5052. This material did not react with aqueous permanganate or alcoholic silver nitrate.

Anal. Calcd. for C_3H_5Br: C, 29.78; H, 4.17; Br, 66.04. Found: C, 30.04; H, 4.23; Br, 65.90.

Similar runs using tetrachloroethane as solvent at −20 to −25° gave 15–20% of crude cyclopropyl bromide. The products of these runs seemed to contain some chlorine-containing substances (sodium fusion).

In an attempt to prepare cyclopropyl bromide by the von Braun reaction, 15.6 g. (0.097 mole) of bromine was added dropwise over 30 minutes to an ice-cooled stirred solution of 15.5 g. (0.096 mole) of N-cyclopropylbenzamide in 32.3 g. (0.12 mole) of phosphorus tribromide. After the addition was complete, the mixture was heated; however, no distillate was obtained below 150° and the material rapidly resinified with the evolution of hydrogen bromide. In a similar experiment where the mixture was allowed to stand for three hours at 0° and distillation attempted under reduced pressure with a bath temperature below 40° no low-boiling material was obtained. On dilution of the reaction mixture with water, N-cyclopropylbenzamide was recovered almost quantitatively.

Beckmann Rearrangement Studies.—The oxime of cyclopropyl methyl ketone (b.p. 90–92°, 20 mm.) was obtained in essentially quantitative yields in runs up to 12 moles by ether extraction and distillation of the organic product resulting from the reaction of hydroxylamine hydrochloride, ketone and sodium carbonate in a mole ratio of 1.25:1:0.5. About 300 ml. of water was used per mole of ketone and the reaction mixture was refluxed for an hour before the ether extraction.

A. Phosphorus Pentachloride.—A solution of 50 g. (0.5 mole) of cyclopropyl methyl ketoxime in 125 ml. of anhydrous ether was added over 35 minutes to an ice-cooled well-stirred suspension of 60 g. (0.28 mole) of phosphorus pentachloride in 150 ml. of anhydrous ether. The mixture was stirred and allowed to warm to room temperature. After an hour, it was poured into an ice-cold solution of 35 g. of sodium bicarbonate in 500 ml. of water. The resulting mixture was acidic and, after neutralization with sodium hydroxide solution, the ether layer was separated. About 3 g. of oxime was recovered from the ether layer. The aqueous layer was extracted continuously with ether for six days. The ether was distilled and the residue dried by distillation of the water with benzene. Distillation yielded 17.3 g. (35%) of mixed amides, b.p. 128–136° (27 mm.).

B. Benzenesulfonate of Cyclopropyl Methyl Ketoxime.—The following procedure is typical of a large number of runs. Benzenesulfonyl chloride (264 g., 1.5 moles) was added dropwise to a solution of 150 g. (1.5 moles) of cyclopropyl methyl ketoxime and 120 g. (1.5 moles) of pyridine in 400 ml. of anhydrous ether at such a rate as to maintain gentle refluxing. After the addition was complete, the mixture was stirred for 30 minutes and filtered (suction) using a 1-l. separatory funnel as a receiver. The collected pyridine hydrochloride was washed with dry ether and the combined ether solutions evaporated under reduced pressure at room temperature. No heat was applied since the product may decompose violently below 100°. The thick residual benzenesulfonate was then run, in 20-g. portions, into 250-ml. wide-mouthed erlenmeyer flasks. Each portion was dissolved in 20 ml. of acetic acid and 10 ml. of water added. After about 30 seconds, the mixtures warmed spontaneously to the boiling point and boiled briskly for several seconds. The contents of the separate reaction flasks were mixed, neutralized with 6 *N* sodium hydroxide solution and extracted continuously with ether for ten days. The ether was distilled and the residue dried by distillation of the water with benzene. Distillation yielded 120 g. (80%) of mixed amides, b.p. 125–132° (20 mm.).

C. Simultaneous Formation and Rearrangement of the Oxime Benzenesulfonate.—In a 5-l. three-necked flask equipped with stirrer, dropping funnel and reflux condenser were placed 500 g. (6.0 moles) of sodium bicarbonate, 250 g. (2.5 moles) of cyclopropyl methyl ketoxime, 2 l. of water and 1.2 l. of dioxane. The mixture was heated to boiling and 500 g. (2.8 moles) of benzenesulfonyl chloride added dropwise over six hours. The clear yellow solution was cooled and extracted continuously with ether for a total of 24 days. About 62% of the product was obtained in seven days, 35% in ten more days and the balance in the final

(7) The fractionating section of this column was similar to that described by E. A. Naragon and C. J. Lewis, *Ind. Eng. Chem., Anal. Ed.*, **18**, 448 (1946).

(8) V. C. Sekera and C. S. Marvel, THIS JOURNAL, **55**, 345 (1933).

seven days. The ether extract yielded 200 g. (80%) of mixed amides, b.p. 125–150° (21 mm.).

Cyclopropylamine.—The following procedure is typical. A solution of 83.5 g. of potassium hydroxide pellets in 90 ml. of water was added to 74.3 g. (0.75 mole) of the amide mixture (from the benzenesulfonate procedure) dissolved in 300 g. of ethylene glycol. The resulting mixture was heated under a 50-cm. Vigreux column and distillate taken off at such a rate as to keep the head temperature below 55°. A Dry-Ice cooled receiver was used to condense the methylamine formed in the reaction. When the hydrolysis was complete, the head temperature rose to 100° and remained constant. The distillate was fractionated using a 30-cm. Vigreux column with a Dry-Ice cooled reflux condenser until all of the methylamine was removed. The yield of methylamine was 2.5 g. (11%). The higher-boiling materials were fractionated using a 30-cm. stainless-steel helix-packed column and yielded 36.5 g. (85%) of cyclopropylamine, b.p. 50°. The benzamide derivative had m.p. 97.5–98.0° (lit.[9] 99°) after crystallization from alcohol–water.

In an attempt to carry out the hydrolysis of the amide mixture by refluxing with 12 *N* hydrochloric acid, extensive decomposition occurred.

(9) M. J. Schlatter, THIS JOURNAL, **63**, 1733 (1941).

CAMBRIDGE 39, MASS. RECEIVED DECEMBER 29, 1950

[CONTRIBUTION FROM THE KEDZIE CHEMICAL LABORATORY, MICHIGAN STATE COLLEGE]

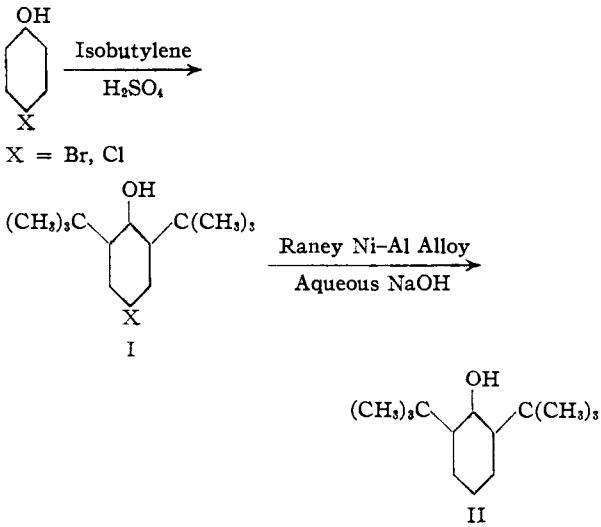
Ortho Alkylated Phenols. 2,6-Di-*t*-butylphenol

BY HAROLD HART AND FRANK A. CASSIS, JR.

In order to study the effect of large substituents ortho to the hydroxyl group on the uncatalyzed alkylation of phenol with *t*-butyl chloride, 2,6-di-*t*-butylphenol was synthesized. Its ultraviolet absorption spectrum and certain of its reactions are described. Nitration at 25–35° in glacial acetic acid (1:1) yielded 4,6-dinitro-2-*t*-butylphenol. Under milder conditions, the oxidation product 3,3′,5,5′-tetra-*t*-butyldiphenoquinone was isolated. Sulfuric acid caused rearrangement to 2,4-di-*t*-butylphenol. The relative rates of alkylation of phenol, 2-*t*-butylphenol, 2,6-di-*t*-butylphenol, *o*-cresol and 2,6-xylenol with *t*-butyl chloride were determined. Possible mechanisms are discussed. The relative rates of alkylation of *m*- and *p*- cresol in the ortho positions are also included.

In order to further elucidate the mechanism of the uncatalyzed alkylation of phenols with tertiary alkyl halides[1] it became desirable to prepare phenols with bulky alkyl groups in the ortho positions but unsubstituted in the para position. Recently[2] the synthesis of 2-*t*-butylphenol in good yield was described. We have now extended this method to the synthesis of 2,6-di-*t*-butylphenol (II) and have studied some of its properties.

Compound II has been reported by Pardee and Weinrich,[3] and Stillson and Sawyer,[4] the latter authors being the only ones to indicate its method of synthesis. However, no indication of yields was given. The general scheme which we used follows our earlier work.[2] The reduction with Raney Ni–Al alloy and aqueous alkali[2,5] afforded a superior yield to the procedure of Stillson and Sawyer,[4] who used potassium and liquid ammonia.[6]



The ultraviolet absorption spectrum of II in cyclohexane is given in Fig. 1, together with that of 2,6-di-*t*-butyl-4-methylphenol for comparison. The peaks at 271 and 278 mμ indicate the absence of any alkyl group in the para position.[2,7]

Nitration of II with concentrated nitric acid in glacial acetic acid (1:1) at room temperature yielded 4,6-dinitro-2-*t*-butylphenol. This product is identical with that obtained by Ipatieff, Pines and Friedman[8] from the nitration of 2,4-di-*t*-butylphenol. In their case, the 4-*t*-butyl group was cleaved from the ring, whereas in the present instance, one of the 2-*t*-butyl groups was cleaved.

An attempt at nitration without cleavage, using 1:6 nitric–acetic acids at 0° yielded small quantities

(1) H. Hart and J. H. Simons, THIS JOURNAL, **71**, 345 (1949).

(2) H. Hart, *ibid.*, **71**, 1966 (1949).

(3) W. A. Pardee and W. Weinrich, *Ind. Eng. Chem.*, **36**, 595 (1944).

(4) G. H. Stillson and D. W. Sawyer, U. S. Patent 2,459,597 (1949); *C. A.*, **43**, 3459 (1949).

(5) D. Papa, E. Schwenk and B. Whitman, *J. Org. Chem.*, **7**, 587 (1942); E. Schwenk, D. Papa, B. Whitman and H. Ginsburg, *ibid.*, **9**, 1 (1944).

(6) Although the product which we obtained affords the correct analysis and expected properties for 2,6-di-*t*-butylphenol, our product was a colorless liquid. We were unsuccessful in crystallizing this material. Stillson and Sawyer[4] and Pardee and Weinrich[3] claim the product to be a yellow solid, m.p. 38–39°. In this connection, it is of considerable interest to note that when I (X = Cl) was reduced with hydrogen in the presence of palladium chloride on charcoal at *room temperature* and 50 atm., a white solid, m.p. 38–38.5° was obtained. This material was shown to be probably 2,6-di-*t*-butylcyclohexanone (private communication from Dr. R. H. Rosenwald, Universal Oil Products Company). The reduction to the cyclohexanone is to be expected (see A. C. Whitaker, THIS JOURNAL, **69**, 2414 (1947)) but the mild conditions which accomplished the reaction are somewhat surprising and bear further investigation. NOTE ADDED IN PROOF: We have recently succeeded in preparing crystalline 2,6-di-*t*-butylphenol. White prisms were obtained from ethanol, m.p. 37-38°. Admixture with some 2,6-di-*t*-butylcyclohexanone obtained from Dr. Rosenwald resulted in immediate liquefaction at room temperature. Preliminary experiments with crystalline II have shown that its rates of bromination in carbon tetrachloride and coupling with diazotized aniline are negligible when compared with 2,6-xylenol.

(7) H. Hart and E. A. Haglund, *J. Org. Chem.*, **15**, 396 (1950).

(8) V. N. Ipatieff, H. Pines and B. S. Friedman, THIS JOURNAL, **60**, 2495 (1938).