[CONTRIBUTION FROM THE CHEMICAL LABORATORIES OF NORTHWESTERN UNIVERSITY]

The Reactions of Some Organometallic Compounds with Cyclohexene Oxide[1]

BY ROBERT L. LETSINGER, JAMES G. TRAYNHAM AND EDWARD BOBKO

Cyclohexenol and low yields of the 2-alkylcyclohexanols were obtained from the reactions of *n*-propyllithium and *n*-butyllithium with cyclohexene oxide. Methyllithium, allylmagnesium bromide and allylsodium reacted with cyclohexene oxide to give good yields of the corresponding 2-substituted cyclohexanols.

Aryllithium compounds[2,3] and dialkylmagnesium compounds[4] react with cyclohexene oxide to give (after hydrolysis) 2-substituted cyclohexanols. Under similar conditions, however, organomagnesium halides cause a contraction of the six-membered ring and produce alkyl (or aryl) cyclopentylcarbinols.[2,5] The magnesium halide appears to be responsible for this rearrangement. Benzylmagnesium chloride is exceptional in that it reacts with cyclohexene oxide by direct displacement to give a 50% yield of 2-benzylcyclohexanol.[2]

In the course of preparing some alkylcyclohexanols it was observed that the reaction of an alkyllithium compound with cyclohexene oxide may take a somewhat different course from that reported for the aryllithium reagents. Thus the yields of 2-alkylcyclohexanols from the reactions of propyllithium and butyllithium were low (13 and 15%, respectively), and the major product from both reactions was 2-cyclohexenol. This alcohol was characterized by the phenylurethan and α-naphthylurethan derivatives, by oxidation to 2-cyclohexenone and by reduction to cyclohexanol. Small amounts of other substances, including some high boiling compounds and traces of cyclohexanone, were also found as products of the reactions of these alkyllithium compounds.

Bedos[6] isolated cyclohexenol from a reaction of phenylmagnesium bromide and cyclohexene oxide that was worked up by distilling the ether solvent prior to the addition of water. When the reaction mixture was hydrolyzed before removing the ether, the products were 2-bromocyclohexanol and cyclopentylphenylcarbinol. It is not clear whether the alcohol originated by the action of a base on cyclohexene oxide or on the bromohydrin, as suggested by Bedos. In the case of the organolithium compounds, however, the possibility that the reaction must involve an intermediate bromohydrin can be definitely excluded, since cyclohexenol (26%) was obtained from a reaction of cyclohexene oxide with a butyllithium solution that was free of lithium halide.

The transformation of cyclohexene oxide into cyclohexenol corresponds to a typical β-elimination reaction. Alkyl ethers[7] are cleaved by organolithium compounds in an analogous way, but at a slower rate. The enhanced reactivity of the three membered oxide ring may therefore be manifested in the elimination as well as in the displacement reaction. It is interesting that methyllithium, which cleaves ethyl ether very slowly if at all,[8] reacted with cyclohexene oxide to give 2-methylcyclohexanol and no detectable cyclohexenol.

In conjunction with these experiments, the reactions of allylmagnesium bromide and allylsodium with cyclohexene oxide were examined. 2-Allylcyclohexanol, characterized by the preparation of a number of solid derivatives, was isolated in good yields from both reactions. The formation of a normal product, rather than a cyclopentylcarbinol or cyclohexenol, is in accord with the previously observed facility with which allylmetallic compounds enter into displacement reactions.[9]

Experimental

Propyllithium Reaction.—Cyclohexene oxide[10] (19.6 g., 0.20 mole) was added dropwise to a filtered solution of propyllithium (prepared from 1.2 g. atom of lithium and 0.50 mole of propyl bromide) in 200 ml. of ether at 0°. After the solution had stirred for an hour at this temperature it was warmed to room temperature and left standing overnight in a nitrogen atmosphere. The next day it was decomposed with water, and the aqueous layer extracted twice with ether. The combined ether portions, after drying, were distilled to give 0.6 g. of unreacted cyclohexene oxide; 11.5 g. of crude 2-cyclohexenol, b.p. 51–53° (4 mm.), $n^{21}\text{D}$ 1.4785; and 3.6 g. (13%) of 2-propylcyclohexanol, b.p. 65–72° (3 mm.), $n^{21}\text{D}$ 1.4650, m.p. of the phenylurethan 65–66° (m.p. reported for the *trans*-isomer, 69–70°[11]). On redistillation of the cyclohexenol fraction 9.8 g. (50%) of a somewhat higher purity product was obtained; $n^{21}\text{D}$ 1.4808 (reported for 2-cyclohexenol, $n^{23}\text{D}$ 1.4860[12]). The phenylurethan derivative melted at 104–105° (reported for derivative of cyclohexenol, 106–107°[13]) and the α-naphthylurethan melted at 153–153.5° (reported m.p. 156°[14]). The cyclohexenol (a 6-g. portion) was further characterized by oxidation with potassium dichromate by the procedure of Kotz and Richter[15] to 2-cyclohexenone; weight 1.5 g., b.p. 67–70° (21 mm.), m.p. of the 2,4-dinitrophenylhydrazone, 162–163° (reported, 163[13] and 116–117[16]).

Butyllithium Reaction (a). (In presence of lithium bromide.)—A mixture of cyclohexene oxide (24.5 g., 0.25 mole) and 370 cc. of 1.31 *N* butyllithium in ether was refluxed for 25 hours. At the end of this time the solution was poured onto ice, and the organic layer separated and dried. On distillation at 20 mm. there was obtained a forerun (18.9 g., b.p. 40–84°), 2-butylcyclohexanol (5.9 g.

---

[1] A portion of this work was supported by the Abbott Fund of Northwestern University.

[2] J. W. Cook, C. L. Hewett and C. A. Lawrence, *J. Chem. Soc.*, 71 (1936).

[3] B. C. McKusick, THIS JOURNAL, **70**, 1976 (1948).

[4] P. D. Bartlett and C. M. Berry, *ibid.*, **56**, 2683 (1934).

[5] (a) M. Vavon and V. M. Mitchovitch, *Compt. rend.*, **186**, 702 (1928); (b) M. Godchot and G. Cauquil, *ibid.*, **186**, 375, 955 (1928); (c) P. Bedos, *ibid.*, **189**, 255 (1929).

[6] P. Bedos, *ibid.*, **177**, 112 (1923); *Bull. soc. chim. France*, [4] **39**, 292, 300 (1926).

[7] R. L. Letsinger, A. W. Schnizer and E. Bobko, THIS JOURNAL, **73**, 5708 (1951).

[8] H. Gilman, F. W. Moore and O. Bain, *ibid.*, **63**, 2479 (1941).

[9] R. L. Letsinger and J. G. Traynham, *ibid.*, **70**, 3342 (1948); **72**, 849 (1950).

[10] "Organic Syntheses," Coll. Vol. I, 2nd Ed., John Wiley and Sons, Inc., New York, N. Y., p. 185.

[11] G. Vavon and P. Anziani, *Bull. soc. chim. France*, [4] **41**, 1642 (1927).

[12] A. Guillemonat, *Compt. rend.*, **205**, 67 (1937).

[13] P. D. Bartlett and G. F. Woods, THIS JOURNAL, **62**, 2933 (1940).

[14] R. Willstätter and E. Sonnenfeld, *Ber.*, **46**, 2957 (1913).

[15] A. Kotz and K. Richter, *J. prakt. Chem.*, [2] **111**, 398 (1925).

[16] F. C. Whitmore and G. W. Pedlow, THIS JOURNAL, **63**, 758 (1941).

or 15%, b.p. 115–118°, n^{25}D 1.4627) and a residue of higher boiling material (3.8 g.). The phenylurethan derivative of the butylcyclohexanol melted at 62–64° (m.p. reported for the *trans*-isomer, 64–65°).[17] Redistillation of the fore-run at atmospheric pressure yielded 13.9 g. of material boiling at 160–162°, n^{25}D 1.4755. On redistillation of this fraction at 30 mm., the following fractions were obtained.

TABLE I

Fraction	B.p., °C.	G.	n^{24}D
1	72–74	1.0	1.4590
2	74–75	2.6	1.4665
3	75–81	2.8	1.4764
4	81–82	6.4	1.4828

Fraction 4 corresponds to a 26% yield of cyclohexenol. The actual yield was somewhat higher as fractions 2 and 3 also contained some cyclohexenol. Thus fraction 2, as well as fraction 4, gave a phenylurethan derivative of this alcohol (m.p. of derivative of 4, 105–106°, m.p. of derivative 2, 104–105°).

Fractions 1–3 gave small amounts of precipitate with 2,4-dinitrophenylhydrazine reagent,[18] but neither 4 nor the cyclohexene oxide used as a reagent for the butyllithium reaction gave a precipitate under similar conditions. The melting point of the derivative of 2 was 158.5–159°, and it was not depressed when the sample was mixed with an authentic sample of cyclohexanone 2,4-dinitrophenylhydrazone. The cyclohexanone was present in only small amounts, however, for this test is quite sensitive and none of the fractions gave a precipitate with a saturated solution of sodium bisulfite. For comparison purposes, it was found that a few drops of a 13% solution of cyclohexanone in cyclohexanol readily gave a precipitate under these conditions. Cyclohexanone, therefore, should represent not more than 3% of the total reaction, and it probably amounted to only a very small fraction of this percentage. The formation of cyclohexanone presumably involved the attack of the base on an α-hydrogen atom, rather than on a β-hydrogen or α-carbon atom. An isomerism of this type has been reported to occur when cyclohexene oxide is treated with sodium or sodamide.[19]

(b) (In absence of lithium bromide).—Butyllithium was prepared in 86% yield from 1.8 g. of lithium raspings and 0.6 mole of *n*-butyl bromide in 450 cc. of pentane. The solution was filtered through a sintered glass filter in order to remove the lithium bromide and other insoluble lithium salts and then mixed with a solution of 19.3 g. of cyclohexene oxide in 50 cc. of ether. After a 22-hour period of refluxing this solution was poured onto ice and water, and the organic portion (together with ether extracts of the aqueous layer) separated, dried over calcium sulfate and distilled. There was obtained 11.04 g. of material boiling at 60–90° (20 mm.), n^{21}D 1.4747; and 2.20 g. (7.1%) of a butylcyclohexanol fraction boiling at 113–120°; n^{21}D 1.4640. Redistillation of the lower boiling material gave the following fractions (at 24 mm.).

TABLE II

Fraction	G.	B.p., °C.	n^{22}D
1	0.22	42–70	1.4650
2	3.51	70–73	1.4677
3	4.96	74–78	1.4825

Almost all of fraction 3 boiled at 76.5–77.5°.

In a quantitative microhydrogenation it was found that fraction 3 took up 95% of a mole equivalent of hydrogen (on the assumption that 3 was pure cyclohexenol) whereas fraction 2 similarly absorbed 57% of a mole equivalent of hydrogen. Cyclohexanol (m.p. of phenylurethan derivative, 80–81°) was obtained as the reduction product of fraction 3. The yield of cyclohexenol represented by the material in 3 is 26%; that calculated on the assumption that the unsaturation in 2 also represents cyclohexenol is 36%.

Methyllithium Reaction.—Cyclohexene oxide (20.5 g., 0.21 mole) and 300 cc. of a filtered ether solution of 0.83 *N* methyllithium (0.25 mole) were permitted to react under the same conditions that were used for the butyllithium reaction (a). The products were distilled at 30 mm. and the lower boiling portions redistilled at atmospheric pressure. None of the fractions showed unsaturation in a bromine test. There was obtained 14.95 (63%) of 2-methylcyclohexanol, b.p. 160–163°, n^{25}D 1.4606. A portion was refractionated through a Vigreux column at 29 mm.; b.p. of a middle cut, 80.6–81°; n^{25}D 1.4605.

The properties of the alcohol (160–163°) and its derivations are compared with *cis* and *trans* 2-methylcyclohexanol and their derivatives in Table III. It is apparent that considerable amounts of the *cis* alcohol were present in the reaction product, in contrast to the results from the reaction of dimethylmagnesium and cyclohexene oxide.[4] It was not established, however, whether the *cis* isomer was formed by a direct reaction of methyllithium with the oxide, or resulted from a subsequent isomerization of *trans*-2-methylcyclohexanol.

TABLE III

	Reaction product	2-Methylcyclohexanol[20] *cis*	*trans*
n^{25}D (alcohol)	1.4606	1.4616	1.4596
M.p. phenylurethan	94.5–95.5[a]	93–94	104–105[21]
M.p. acid phthalate	89–90.5[a,b]	89–90	124–125

[a] Several recrystallizations were necessary to obtain the materials melting within this range. [b] *Anal.* (by C. Brauer). Calcd. for $C_{15}H_{18}O_4$: C, 68.68; H, 6.92. Found: C, 68.71; H, 6.62.

Allylmagnesium Bromide Reaction.—An ether solution of cyclohexene oxide (24.5 g., 0.25 mole) and allylmagnesium bromide (from 1.5 g. atom of magnesium and 0.75 mole of allyl bromide) was refluxed for 14 hours. Conventional work-up and distillation at 17 mm. gave 1.5 g. of material boiling at 60–90°, 1.9 g. at 90–95° and 29.0 g. at 95–100°. All fractions gave a positive Beilstein test but were less dense than water. Redistillation failed to remove the halogen impurity. Since it seemed likely that the source of halogen was bromocyclohexanol, a portion (28.4 g., b.p. 95–97° (16 mm.), n^{27}D 1.4780) was stirred vigorously for one hour with 5 g. of sodium hydroxide in 30 cc. of water. On recovery of the organic material, drying and distillation, there was obtained 22.5 g. (64%) of halogen free product, b.p. 94–96° (15 mm.); n^{27}D 1.4757. This substance was identified as 2-allylcyclohexanol by the following experiments.

(a) A 2.0-g. sample was reduced with hydrogen over platinum in methanol to 2-propylcyclohexanol. One mole equivalent of hydrogen was taken up, and the reduced product (1.7 g., b.p. 95° at 14 mm., n^{25}D 1.4608) gave a phenylurethan which melted at 66.5–67.5°.

(b) A solution of 10.0 g. of the product was hydrogenated over platinum in acetic acid. To the filtered solution was then added dropwise a solution of 6.0 g. of chromic anhydride in 25 cc. of 80% acetic acid. The following day the dark blue solution was diluted to 500 cc. with water and twice extracted with ether. From this was obtained 7.0 g. (70%) of ketone, b.p. 94–95° (25 mm.); n^{27}D 1.4492. The oxime melted at 66.5–67° (reported for 2-propylcyclohexanone oxime, 67–68°)[11] and the 2,4-dinitrophenylhydrazone melted at 149.5–150° (not previously reported). It was surprising that the semicarbazone melted at 110–111°, for the reported m.p. for 2-propylcyclohexanone semicarbazone was 130°[22] (and 134°[11]).

As confirmation of these derivatives, propylcyclohexanone was prepared independently by catalytically (with hydrogen over platinum) reducing 2-allylcyclohexanone obtained by allylation of cyclohexanone.[23] A 92% yield of 2-propyl-

---

(17) G. Vavon and A. Gueden, *Bull. soc. chim. France,* [4] **47,** 901 (1930).

(18) R. L. Shriner and R. C. Fuson, "Identification of Organic Compounds," 3rd ed., John Wiley and Sons, Inc., New York, N. Y., 1948, p. 171.

(19) M. Mousseron and co-workers, *Bull. soc. chim. France,* [5] **12,** 238 (1945); **13,** 629 (1946).

(20) G. A. Gough, H. Hunter and J. Kenyon, *J. Chem. Soc.,* 2061 (1926).

(21) G. Vavon, A. Perkin and A. Horeau, *Bull. soc. chim. France,* [4], **51,** 644 (1932).

(22) M. Tiffeneau, B. Tchoubon and Saias-Lambert, *ibid.,* [5] **14,** 448 (1947).

(23) *Org. Syntheses,* **28,** 8 (1948).

cyclohexanone was obtained; b.p. 105–107° (42 mm.), $n^{25}D$ 1.4515. The melting point of the derivatives of the ketone thus prepared were: oxime, 66–66.5°, 2,4-dinitrophenylhydrazone, 147–148°; and semicarbazone, 111–112°. Mixed melting points taken with these derivatives and those from the product of the Grignard reaction showed no depression.

Allylsodium Reaction.—To a stirred suspension of allylsodium[9] (prepared from 17.3 g., 0.75 g. atom of sodium and 39.2 g., 0.40 mole of allyl ether) in petroleum ether (b.p. 60–71°) at 0° was added dropwise 27.5 g. (0.28 mole) of cyclohexene oxide. The mixture was stirred 20 minutes at 0°, allowed to warm to 25° over an hour period, stirred for two additional hours at this temperature, and carbonated on Dry Ice. Water was then added and the mixture extracted with ether. The ether extracts yielded on distillation (22 mm.) 14.1 g. of material boiling at 99–104.5° and 19.5 g. at 104.5–105.5° (total yield represented by both fractions, 85%). These two fractions were independently reduced and oxidized as in the case of the product from the Grignard reaction. The melting points of the derivatives of propylcyclohexanone thus obtained were: oxime, 65.5–66°, 2,4-dinitrophenylhydrazone 149–150°, semicarbazone 111–114°. The semicarbazones were prepared several times. In most cases the melting points were in the region of 111°, but in a few cases were found as high as 120°, and in one case a melting point of 130° was obtained.

EVANSTON, ILLINOIS RECEIVED AUGUST 15, 1951

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE UNIVERSITY OF CALIFORNIA]

2-(2-Hydroxyphenoxy)-benzoic Acid Lactone, a Simple Analog of the Depsidones[1]

BY DONALD S. NOYCE AND JOHN W. WELDON

Depsidones, analogs of 2-(2-hydroxyphenoxy)-benzoic acid lactone have been reported to have bacteriostatic activity. The synthesis of the basic ring system and a brief study of its reactivity are reported.

A wide variety of compounds have been isolated from lichens. Many have been shown to be highly substituted derivatives of 2-(2-hydroxyphenoxy)-benzoic acid lactone (I) and have been given the generic name "depsidone."[2] Bacteriostatic activity has recently been reported for a number of compounds from lichens,[3,4,5] including usnic acid[3] and the depsidones, diploicin[4] and physodic acid.[5]

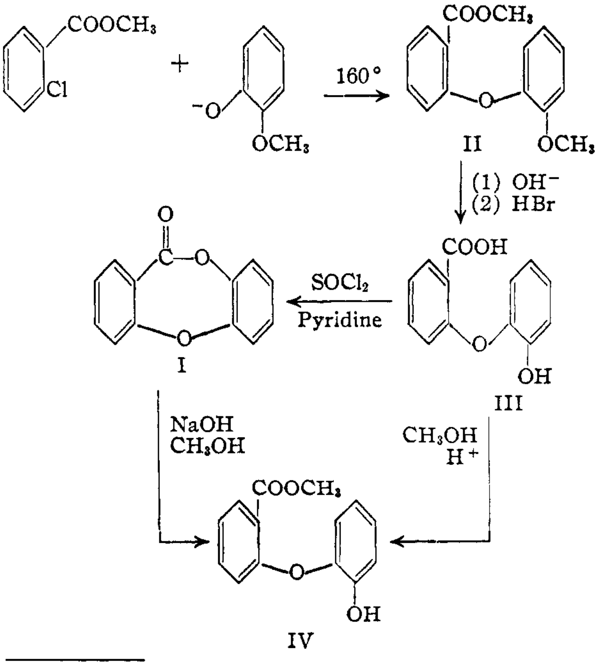
Since no compounds possessing the basic nucleus of the depsidones have apparently been synthesized, we have undertaken an investigation of applicable methods for synthesis of such systems. The most attractive method might appear to be the peroxy acid oxidation[6] of xanthone. However, this oxidation failed under a wide variety of experimental conditions. This failure must be attributed at least partially to the lack of reactivity of the carbonyl group of xanthone as influenced by the conjugated ether bridge, since fluorenone is oxidized smoothly to 2-(2-hydroxyphenyl)-benzoic acid lactone.[7] Similar attempts to oxidize 3-methoxyxanthone and 2-nitroxanthone with peracetic acid also failed.

The alternate approach to I involved lactonization of the appropriate hydroxy acid. Two other seven-membered dibenzlactones have been previously prepared by ring closure. Orndorff and Kline[8] have prepared the lactone of 2-(2,4-dihydroxybenzoyl)-benzoic acid using acetic anhydride, while Galbraith and Smiles[9] have prepared the lactone of 2-(2-hydroxy-5-methylphenylmercapto)-5-nitrobenzoic acid by a similar procedure.

In the present investigation condensation of methyl *o*-chlorobenzoate with sodium guaiacolate in the presence of catalytic amounts of copper powder resulted in methyl 2-(2-methoxyphenoxy)-benzoate (II) in 65% of the theoretical amount. Koelsch[10] and Ullmann[11] have reported somewhat lower yields in a similar condensation using sodium *o*-chlorobenzoate. Hydrolysis of II and demethylation with hydrogen bromide in acetic acid yielded the desired hydroxy acid (III) in 83% yield.

Lactonization of III to I was accomplished in several manners. By the use of acetic anhydride 70% of the theoretical amount of I was obtained. Less satisfactory were the use of β-naphthalenesulfonic acid as a catalyst in a high dilution procedure[12]

CHART I



---

[1] From the Ph.D. dissertation submitted by John W. Weldon at the Graduate Division of the University of California, 1951.

[2] Y. Asahina, *Acta Phytochim.* (*Japan*), **8**, 33 (1934).

[3] A. Marshak, *U. S. Pub. Health Repts.*, **62**, 3 (1947); A. Marshko, G. T. Barry and L. C. Craig, *Science*, **106**, 394 (1947).

[4] V. C. Barry, *Nature*, **158**, 131 (1946).

[5] A. Stoll, J. Renz and A. Brack, *Experientia*, **3**, 111 (1947).

[6] *Cf.* W. Dilthey, M. Inkel and H. Stephan, *J. prakt. Chem.*, **154**, 219 (1939); J. E. Leffler, *Chem. Revs.*, **45**, 385 (1949).

[7] G. Wittig and G. Pieper, *Ber.*, **73**, 295 (1940).

[8] W. R. Orndorff and E. Kline, THIS JOURNAL, **46**, 2283 (1924).

[9] F. Galbraith and S. Smiles, *J. Chem. Soc.*, 1234 (1935).

[10] C. F. Koelsch and F. J. Flucht, THIS JOURNAL, **71**, 3556 (1949).

[11] F. Ullmann and M. Zlokasoff, *Ber.*, **38**, 2118 (1905).

[12] M. Stoll and A. Rouve, *Helv. Chim. Acta*, **18**, 1087 (1935).