[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, IOWA STATE COLLEGE]

Cleavage of Phenoxathiin-10-oxide by *n*-Butyllithium

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The interaction of phenoxathiin-10-oxide with *n*-butyllithium at −50°, followed by carbonation. produced 2-carboxydiphenyl ether, 2,2′-dicarboxydiphenyl ether, *n*-butyl mercaptan, diphenyl ether, phenoxathiin and 1-phenoxathiincarboxylic acid. At higher temperatures only the last three compounds were isolated. A mode of reaction for the metalation is proposed.

In the course of the study of the reactions of phenoxathiin-10-oxide (I) it was found that *n*-butyllithium cleaves the compound at low temperatures. Phenoxathiin (II) has been metalated in the 4-position by *n*-butyllithium[1] and has been cleaved by sodium in liquid ammonia.[2] However, the cleavage reaction reported herein differs in that it involves removal of sulfur from the cleaved compound. Shirley and Lehto[3] reported that the reaction of phenoxathiin-10-oxide with three equivalents of *n*-butyllithium at −20° for five hours, followed by a one-hour period in which the mixture was allowed to warm to room temperature prior to carbonation, produced a 22% yield of 1-phenoxathiincarboxylic acid (III). On the basis of the absence of metalation of dibenzothiophene at low temperature[4] and the position of metalation of phenoxathiin-10-oxide it has been postulated[3,4] that the sulfoxide group must be intact at the time of low temperature metalation *ortho* to the carbon–sulfur linkage, *i.e.*, metalation precedes reduction.

An attempt was made to investigate the postulate and the intermediate course of the reaction and to determine the necessity of using three equivalents of *n*-butyllithium. It appeared feasible that if metalation preceded reduction and that if the metalated phenoxathiin-10-oxide were a sufficiently stable intermediate, this organometallic compound could be derivatized by carbonation and 1-phenoxathiincarboxylic acid 10-oxide would be produced. The expected acid was not isolated, but from the reaction of one equivalent of *n*-butyllithium and phenoxathiin-10-oxide at −50° there were obtained phenoxathiin, 1-phenoxathiincarboxylic acid and the cleavage products, diphenyl ether (IV) and 2-carboxydiphenyl ether (V). When two and three equivalents of *n*-butyllithium were employed at −50°, the additional products, 2,2′-dicarboxydiphenyl ether (VI) and *n*-butyl mercaptan, were isolated (see equation 1 and Table I). Subsequently, the reaction was carried out under the conditions described by Shirley and Lehto[3] and a yield of 1-phenoxathiincarboxylic acid comparable to that reported by these authors was obtained. Also, it was found that two equivalents of *n*-butyllithium at −20° to room temperature produced a moderate yield of 1-phenoxathiincarboxylic acid. In addition there were isolated diphenyl ether and phenoxathiin from the mixture.

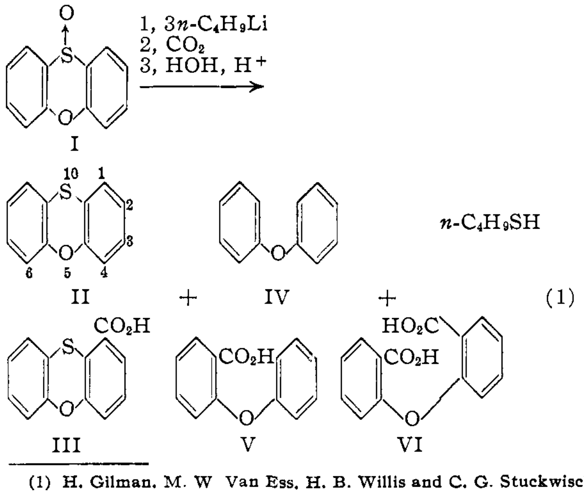

TABLE I

Equivalents[f] of $n\text{-}C_4H_9Li$	Products, % II	III	IV	V	VI	$n\text{-}C_4H_9SH$
1	37	4	18	8	...	[a]
2	14[b]	2	[a]	[a]	37[c]	[d]
2	19[b]	2	[a]	15	13	[a]
3	17	1	[a]	[a]	36[c]	13
3	25	6	14	12	17	7
3	12[b]	[a]	[a]	[a]	31[c]	[a]
1[g]	49[b]	..	[a]	..	...	..
2[g]	14	16	42	..	...	..
3[g]	[e]	21	[e]	..	...	..

[a] No isolation attempt made. [b] Separated from IV by crystallization. [c] High yield believed due to rapid addition of n-C_4H_9Li to a concentrated mixture. [d] Distilled as an azeotrope; derivatized, but not isolated quantitatively. [e] A large amount of oil remained after removal of extraction solvent. Separation into II and IV by vacuum distillation not attempted. [f] Reactions at −50° except where noted. [g] Reaction at −20, 20°.

A comparison of the yields at the two temperatures reveals approximately the same amount of cleavage, but more metalation of the heterocycle at the higher temperature. However, the yield of 1-phenoxathiincarboxylic acid was not increased by carrying out the reaction at temperatures higher than that used by Shirley and Lehto.

A reaction similar to the cleavage of phenoxathiin-10-oxide occurs when the related heterocycle, thianthrene-10-oxide, is treated with *n*-butyllithium at low temperatures to produce thianthrene, 1-thianthrenecarboxylic acid, 2,2′-dicarboxydiphenyl sulfide and dibenzothiophene.[5] Despite repeated attempts, there was isolated none of the analogous dibenzofuran from the phenoxathiin-10-oxide reaction.

The cleavage may have been initiated by an at-

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(1) H. Gilman, M. W Van Ess, H. B. Willis and C. G. Stuckwisch, THIS JOURNAL, **62**, 2606 (1940).

(2) M. Tomita, Y. Inubushi and H. Niwa, *J. Pharm. Soc. Japan*, **72**, 206 (1952) [*C. A.*, **47**, 6428 (1953)].

(3) D A Shirley and E. A. Lehto, THIS JOURNAL, **77**, 1841 (1955).

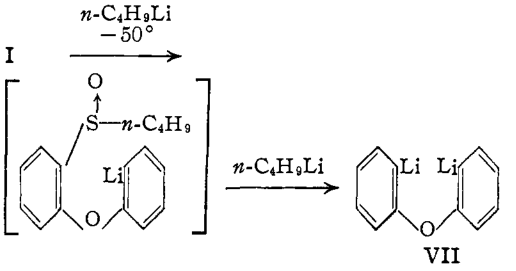
(4) H. Gilman and D. L. Esmay, *ibid.*, **74**, 266 (1952).

(5) H. Gilman and D. R. Swayampati, *ibid.*, **77**, 3387 (1955).

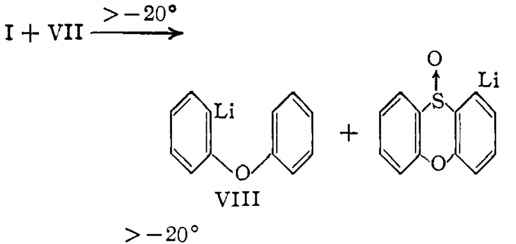
tack of the butyl carbanion on sulfur. A similar mechanism has been proposed to explain the production of lithium mercaptides from the reaction of organolithium compounds with thiacyclopropanes and thiacyclobutanes.[6] In order to prove that the formation of lithiodiphenyl ethers did not occur by way of a two-step process involving cleavage followed by metalation, the action of *n*-butyllithium on diphenyl ether at −50° was investigated. No metalation took place at this temperature.

Any cleavage of the heterocycle would be expected to produce 2,2′-dilithio- (VII) or 2-lithio diphenyl ether (VIII) or a lithio derivative similar to the intermediate in equation 2. These organometallic compounds would yield carboxylic acids upon carbonation. Appreciable amounts of the acids corresponding to the first two lithium compounds were isolated, but only when the metalation reactions were carried out at −50°. At the higher temperatures the lithium atoms were apparently replaced by hydrogen prior to the carbonation reaction. Since the absence of the carboxydiphenyl ethers paralleled the formation of 1-phenoxathiincarboxylic acid, it appeared that 2-lithio- or 2,2′-dilithiodiphenyl ether may have metalated phenoxathiin-10-oxide. The cleavage and metalation reactions are illustrated by equations 2–4.

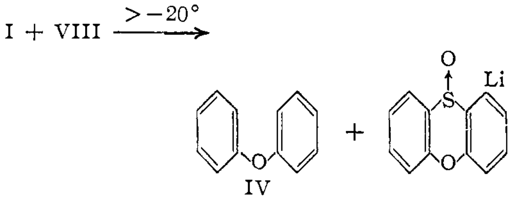
The metalation reactions may not occur to a significant extent until the mixture is allowed to warm above −20°. Such a situation would explain the presence of large amounts of the carboxydiphenyl ethers, yet little of 1-phenoxathiincarboxylic acid when the reaction mixture was carbonated after a short reaction period at low temperature.



(2)



(3)



(4)

The mode of reaction for the metalation was tested by adding a mixture of 2-lithio- and 2,2′-dilithiodiphenyl ether to phenoxathiin-10-oxide at −20° and allowing the reaction mixture to warm to room temperature before carbonation. The isolated quantity of 1-phenoxathiincarboxylic acid 10-oxide was small, but sufficient to give support to the postulated mode of reaction. This acid may have been formed by a reaction such as is illustrated by equation 3 or 4. Since no 1-phenoxathiincarboxylic acid was isolated, it appears that reduction of the metalated compound is effected by *n*-butyllithium, but not by the lithiodiphenyl ethers.

The structural or electronic property responsible for the suspected metalation activity of the lithiodiphenyl ethers is not known. The activity may be due to the ether linkage or may be a general property of aryllithium reagents. It is believed that phenyllithium effects less cleavage and less reduction of phenoxathiin-10-oxide than does *n*-butyllithium.

The isolated 2-carboxydiphenyl ether may have resulted from the 2-lithiodiphenyl ether which was originally present in the mixture or from that which may have been produced by the reaction illustrated by equation 3. Since the lithiodiphenyl ethers were prepared by metalation of diphenyl ether, this uncertainty was unavoidable.

Experimental[7]

Cleavage of Phenoxathiin-10-oxide (I). (a) Three Equivalents at −50°.—To a stirred suspension of 43.3 g. (0.20 mole) of phenoxathiin-10-oxide in 350 ml. of anhydrous ether at −50° was added 543 ml. of a 1.18 *M* ether solution (0.64 mole) of *n*-butyllithium[8] over a period of 45 minutes. All the solid had dissolved after the second equivalent had been added. Color Test I[9] was positive throughout, but Color Test II[10] became positive only after the addition of the third equivalent and remained positive after 45 minutes at −50 ± 5°. The mixture was poured into a stirred slurry of Dry Ice and ether. After the ether had evaporated the solid carbonation mixture was extracted for 24 hours in a Soxhlet extractor with petroleum ether (b.p. 60–70°). The extract was dried and the solvent distilled. The residue was distilled at 1.0 mm. to yield 4.6 g. (13.5%) of diphenyl ether, b.p. 78–80°, and 9.8 g. (24.5%) of phenoxathiin, b.p. 120–121°, m.p. and mixed m.p. with an authentic sample 56–57°. The identity of the diphenyl ether was proven by conversion to 4,4′-dibromodiphenyl ether. This bromination product showed no depression in m.p. (59–60°) with an authentic specimen. The solid from the Soxhlet thimble was stirred with water, the mixture filtered and the yellow aqueous solution extracted with ether to remove oily material. Following removal of dissolved ether from the salt solution, the latter was stirred with Norit-A, filtered, and acidified with dilute hydrochloric acid. The sticky acid was collected and the filtrate saturated with sodium chloride and extracted with pentane. The acid was dissolved in dilute alkali and reprecipitated from the salt solution twice, the aqueous filtrate being extracted with pentane both times. The solid acid was stirred with 150 ml. of warm benzene, the mixture allowed to cool and then filtered to yield 9.8 g. of white solid, melting range 220–227°. After crystallization from methyl ethyl ketone there was obtained 8.6 g. (16.7%) of 2,2′-dicarboxydiphenyl ether, m.p. and mixed m.p. with an authentic specimen,[11] 229–230°. The benzene solution was extracted with four 75-ml. portions of 5% sodium hydroxide solution and the warm extract was acidified. The acidic mixture

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(6) F. G. Bordwell, H. M. Andersen and B. M. Pitt, This Journal, **76**, 1082 (1954).

(7) All melting points are uncorrected. All reactions involving organometallic compounds were carried out in an atmosphere of dry, oxygen-free nitrogen.

(8) H. Gilman, J. A. Beel, C. G. Brannen, M. W. Bullock, G. E. Dunn and L. S. Miller, This Journal, **71**, 1499 (1949).

(9) H. Gilman and F. Schulze, *ibid.*, **47**, 2002 (1925).

(10) H. Gilman and J. Swiss, *ibid.*, **62**, 1847 (1940).

(11) Kindly provided by Dr. R. H. F. Manske.

was boiled and the supernatant liquid filtered. Extraction was repeated 5 times with 200-ml. portions of hot water. Following cooling and filtration there was obtained 6.4 g. of solid melting over the range 98–103°. The product was recrystallized from hot water to yield 4.9 g. (11.5%) of 2-carboxydiphenyl ether, m.p. and mixed m.p. 113–114°. The residue from the hot water extraction was washed with petroleum ether (b.p. 60–70°) and then crystallized twice from dilute acetic acid to yield 2.7 g. (5.5%) of 1-phenoxathiincarboxylic acid,[12] m.p. and mixed m.p. 223–224.5°. Distillation of the pentane extract of the acidic, aqueous filtrate yielded 1.2 g. (6.7%) of *n*-butyl mercaptan (b.p. 82–86°), characterized as the mercury salt which did not depress the m.p. of an authentic specimen of mercury di-*n*-butyl mercaptide (85–86°).[13]

(b) **Two Equivalents at −50°.**—To a stirred suspension of 32.4 g. (0.15 mole) of phenoxathiin-10-oxide in 300 ml. of anhydrous ether at −50° was added 288 ml. of a 1.10 *M* ether solution (0.32 mole) of *n*-butyllithium over a period of 1 hour. The mixture was stirred at −50° for 20 minutes and then carbonated. By working up the carbonation mixture as described in (a), except that phenoxathiin was isolated by crystallization and no attempt was made to isolate the diphenyl ether or the mercaptan, there were obtained 5.8 g. (19.3%) of phenoxathiin, 5.1 g. (13.2%) of 2,2'-dicarboxydiphenyl ether, 3.7 g. (15.1%) of 2-carboxydiphenyl ether and 0.7 g. (1.9%) of 1-phenoxathiincarboxylic acid.

(c) **One Equivalent at −50°.**—To a stirred suspension of 21.6 g. (0.10 mole) of phenoxathiin-10-oxide in 200 ml. of anhydrous ether at −50° was added 81 ml. of a 1.35 *M* ether solution (0.11 mole) of *n*-butyllithium over a period of 15 minutes. After 1 hour of stirring at −50 ± 5° the mixture was carbonated. The procedure described in (a) was employed in the isolation of 3.0 g. (17.6%) of diphenyl ether, 7.4 g. (37.0%) of phenoxathiin, 1.7 g. (8.0%) of 2-carboxydiphenyl ether and 1.0 g. (4.1%) of 1-phenoxathiincarboxylic acid.

(d) **Two Equivalents at −20°, Room Temperature.**—The same procedure was used as in (b) except that the neutral compounds were isolated by vacuum distillation. The *n*-butyllithium solution was added at −20° and the mixture kept at this temperature for 5 hours; then it was allowed to warm to room temperature prior to carbonation. There were obtained 4.2 g. (14.0%) of phenoxathiin, 10.8 g. (42.4%) of diphenyl ether and 5.8 g. (15.8%) of 1-phenoxathiincarboxylic acid. The presence of *n*-butyl mercaptan was not apparent, and thus no attempt was made to isolate it.

Preparation of 2-Lithio- and 2,2'-Dilithiodiphenyl Ether.—To a stirred solution of 28.7 g. (0.166 mole) of diphenyl ether in 200 ml. of anhydrous ether was added 235 ml. of a 1.42 *M* solution (0.333 mole) of *n*-butyllithium and the mixture was refluxed for 130 hours. Color Test II was negative at this time. A 5-ml. aliquot was withdrawn, carbonated and worked up to yield 0.54 g., melting range 115–170°, and 0.16 g., melting range 168–202°. The melting ranges suggested that the product was a mixture of 2-carboxy- and 2,2'-dicarboxydiphenyl ether.[14]

Reaction of Phenoxathiin-10-oxide (I) with 2-Lithio- and 2,2'-Dilithiodiphenyl Ether.—To a stirred suspension of 21.6 g. (0.10 mole) of phenoxathiin-10-oxide in 200 ml. of ether at −20° was added the above-described suspension of 2-lithio- and 2,2'-dilithiodiphenyl ether over a period of 1 hour. After 5 hours at −20 ± 5° the orange-pink mixture was allowed to warm to 20° over a period of 1 hour and then carbonated.

When all the ether had evaporated from the carbonation mixture the dry solid was extracted overnight in a Soxhlet extractor with petroleum ether (b.p. 60–70°). The solvent-free solid from the Soxhlet thimble was stirred with water. The sticky material did not dissolve in water or in ether or in a mixture of the two solvents. After long heating in a mixture of water and acetone, most of the material dissolved and the mixture was filtered. When the filtrate was boiled to remove the acetone, a sticky, reddish-brown material separated. The supernatant salt solution was decanted from the resinous material. The latter, believed to be unreacted phenoxathiin-10-oxide, subsequently came down as an oil after attempted crystallization from ethanol and from benzene.

Into the salt solution, which was treated with Norit-A and filtered, was bubbled carbon dioxide, causing the precipitation of a sticky, tan-colored material. The phenolic material was removed from the mixture by extraction first with benzene and then with ether. Unsuccessful attempts were made to purify the reddish-brown phenolic materials obtained upon concentration of the extracts.

The salt solution, from which phenolic materials had been removed, was heated to expel dissolved solvents and was acidified. There was collected 19.0 g. of product, melting range 100–169°, which was digested with benzene and the mixture was filtered. The insoluble residue weighed 1.5 g. and melted over the range 231–236°, with decomposition. The benzene filtrate was extracted with dilute sodium hydroxide and the extract was acidified to yield 17.0 g. of white solid melting over the range 104–120°. The white solid was extracted with petroleum ether (b.p. 60–70°) in a Soxhlet extractor. After three extractions over an extended period of time, there was obtained from the extract a total of 13.2 g. (61.7% based upon 0.10 mole of 2-lithiodiphenyl ether) of 2-carboxydiphenyl ether, m.p. and mixed m.p. 112–113.5°.

The benzene-insoluble solid which weighed 1.5 g. (melting range 231–236°) was recrystallized from methanol–water (2:1) to yield 0.75 g. of white crystals of 1-phenoxathiincarboxylic acid 10-oxide, m.p. 262°, with decomposition. A mixed melting point with an authentic sample prepared by oxidation of 1-phenoxathiincarboxylic acid was not depressed.

Preparation of 1-Phenoxathiincarboxylic Acid 10-Oxide.—To a yellow, refluxing solution of 2.44 g. (0.01 mole) of 1-phenoxathiincarboxylic acid in 50 ml. of absolute ethanol was added dropwise 6 ml. (0.06 mole) of 30% aqueous hydrogen peroxide. After 3 hours of refluxing an additional 4 ml. of the peroxide was added and the mixture was refluxed for a period of 9 hours. The solvent was distilled until the volume of the residue was 15 ml. and the solution was allowed to cool. The white crystals of 1-phenoxathiincarboxylic acid 10-oxide weighed 2.38 g. (91.5%) and melted at 262°, with decomposition.

Anal. Calcd. for $C_{13}H_8O_4S$: S, 12.32; neut. equiv., 260. Found: S, 12.20, 12.24; neut. equiv., 260, 262.

AMES, IOWA

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[12] An authentic specimen was kindly provided by Dr. D. A. Shirley.

[13] E. Wertheim, THIS JOURNAL, **51**, 3661 (1929).

[14] Mr. K. Oita of this Laboratory found that 2,2-dilithiodiphenyl ether was formed in approximately 60% yield by dimetalation of diphenyl ether.