CLEAVAGE OF XANTHENE ETHERS

A NEW ROUTE TO 9-SUBSTITUTED XANTHENES

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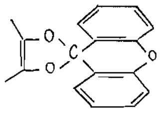
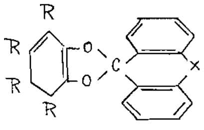
ABSTRACT

9,9-(Tetrachloro-*o*-phenylenedioxy) xanthene (II*a*) and its thio-analogue (II*b*) are cleaved by hydrazines to give the corresponding hydrazones of xanthone and thiaxanthone, respectively, together with tetrachlorocatechol. The unsaturated nitriles (V*a*), (V*b*), and (V*c*) are produced similarly by the action of malononitrile and cyanoacetic ester. Dixanthenyl ether itself reacts in a similar manner with active hydrogen compounds to give the corresponding 9-xanthyl derivatives. (II*b*) is prepared by the action of 9-diazothiaxanthene on tetrachloro-*o*-benzoquinone and is readily cleaved by lithium aluminum hydride to give thiaxanthene and tetrachlorocatechol. The reaction mechanisms are discussed.

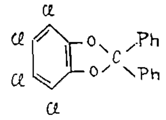
9-Substituted xanthenes have found wide application in biology and industry, and special attention has been directed recently to the study of the chemistry of this group of compounds. It has been shown, in this laboratory, that xanthene ethers of the type (I) have unusual chemical reactivity unrelated to that of previously reported analogous compounds. For example, it is known that ethers are ordinarily not reactive enough as substrate to be hydrolyzed easily; however, it has been found (1) that 9,9-(tetrachloro-*o*-phenylenedioxy) xanthene (II*a*), in contrast to other analogous methylenedioxy derivatives such as (III), is easily cleaved by dilute mineral acids under very mild conditions to give xanthone. Also, it has been reported (2) that xanthene ethers of the type (I) exceptionally undergo reductive cleavage by lithium aluminum hydride yielding xanthene. The unusual reactivity of (I) has been rationalized by assuming that a carbonium ion is first formed as an intermediate and is stabilized by resonance with the unshared electron pair on the oxygen of the xanthylene residue.



(I)



(II*a*): R = Cl, X = O.
(II*b*): R = Cl, X = S.
(II*c*): R = Br, X = S.



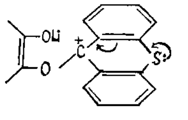
(III)

In the present investigation, it is found that the thiaxanthene analogues have similar reactivity. Thus, when (II*b*) is allowed to react with lithium aluminum hydride in boiling ether, thiaxanthene and tetrachlorocatechol are produced (3). It is assumed that cleavage proceeds by the initial attack of a positive ion such as Li^+ or AlH_2^+ on the oxygen of the dioxole ring followed by the heterolytic fission of the C—O bond to give a resonance stabilized carbonium ion (cf. IV) which readily picks up a hydride ion yielding finally xanthene. A similar mechanism has been previously proposed for the cleavage of the analogous cyclic ether (II*a*) (2). (II*a*) is prepared in good yield by the reaction of 9-diazothiaxanthene with tetrachloro-*o*-benzoquinone. The bromo-analogue (II*c*) is similarly obtained from tetrabromo-*o*-benzoquinone.

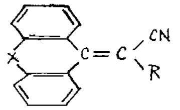
This remarkable reactivity of xanthene and thiaxanthene ethers stimulated us to extend our investigations and study their reactivity towards active hydrogen compounds. It is found (3, 4, 5) that when (II*a*) or (II*b*) is allowed to react with phenylhydrazine or benzoylhydrazine in boiling ethanol, the corresponding hydrazones of xanthone and thiaxanthone, respectively, are obtained together with tetrachlorocatechol. However, with hydrazine hydrate, the corresponding hydrazones and ketazines are produced.

It is found also that malononitrile reacts readily with (II*a*) and (II*b*) under similar conditions to give the highly colored unsaturated dinitriles (V*a*) and (V*b*), respectively, in excellent yields, together with tetrachlorocatechol. However, a higher reaction temperature has been found necessary to cleave the cyclic ether by cyanoacetic ester. For example, (V*c*) is only produced when the higher boiling *n*-butyl alcohol is used as a solvent. (V*a*), (V*b*), and (V*c*) have been previously obtained by condensing malononitrile or ethyl cyanoacetate with the corresponding thione in presence of yellow mercuric oxide (6).

Two possible suggestions might be proposed to explain the production of the xanthylene and thiaxanthylene derivatives by the action of active hydrogen compounds on xanthenic ethers. For example, in the case of the reaction of malononitrile with (II*a*), it is assumed

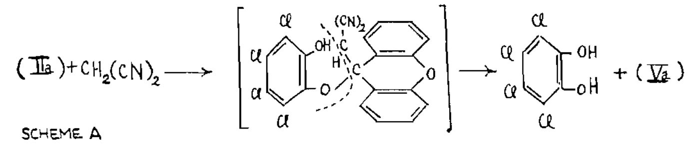


(IV)

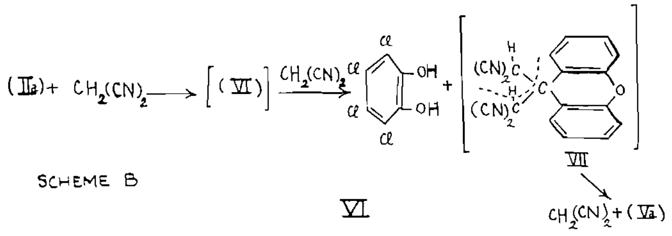


(V*a*): R = CN, X = O.
(V*b*): R = CN, X = S.
(V*c*): R = $OCOC_2H_5$, X = S.

that an intermediate (VI) is first formed which cleaves to give directly Δ^9,α-xanthenemalononitrile by a β-elimination process as shown in Scheme A. The other alternative which immediately suggests itself is that (VI) might react further with another molecule of malononitrile to give a second intermediate (VII) which decomposes under reaction conditions yielding the product as shown in Scheme B. However, the first possibility seems to be more feasible. In this connection, it is worth mentioning that the yield of (V*a*) is found to be the same whether using one or two moles of malononitrile in this reaction.



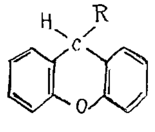
SCHEME A



SCHEME B

The production of the corresponding ketazines in the reaction between (II*a*) or (II*b*) with hydrazine hydrate might be explained by assuming that part of the hydrazone first formed reacts further with the cyclic ether to give the azine. This view is supported by the fact that xanthone hydrazone is found to react readily with (II*a*) under the same conditions to give xanthone azine in excellent yield.

In an attempt to generalize this reaction, the reactivity of dixanthenyl ether itself has been investigated. It is found (4, 5) that the ether reacts readily with active hydrogen compounds to give the corresponding 9-xanthyl derivatives which have been previously obtained by the acid-catalyzed reaction of these compounds with xanthydrol. For example, (VIII*a*), (VIII*b*), and (VIII*c*) are produced, in good yield, by the action of benzoylhydrazine, ethyl cyanoacetate, and malononitrile, respectively, on dixanthenyl ether in boiling ethanol.



(VIII*a*): R = $HN.HNCOC_6H_5$
(VIII*b*): R = $CH.CN.COOC_2H_5$
(VIII*c*): R = $CH(CN)_2$

Cleavage of xanthene ethers by active hydrogen compounds provides a new method for the direct synthesis of 9-substituted xanthenes which enhances the value of xanthene ethers as synthetic intermediates.

EXPERIMENTAL

Reaction of 9,9-(tetrachloro-o-phenylenedioxy) xanthene (IIa) with hydrazine hydrate.—The xanthene ether (1) (1 g) and hydrazine hydrate (98–100%, 1 ml) in absolute alcohol (25 ml) were refluxed together for 5 hours. The solution was filtered while hot, and the orange crystals obtained (0.01 g) were shown to be xanthone azine (m.p. and mixed m.p. 295 °C). The filtrate was concentrated and left to cool. The yellow solid formed was filtered off and recrystallized from methanol to give xanthone hydrazone (0.1 g) m.p. 126 °C (undepressed when admixed with an authentic sample). The main ethanolic mother liquor was poured onto ice-cold water and acidified with hydrochloric acid. The precipitate formed was filtered off, dried, and refluxed with acetic anhydride (10 ml) for 30 minutes. The solution was left to cool, poured onto ice, and the separated solid was filtered off and washed with water. This was dried and crystallized from methanol to give the diacetate of tetrachlorocatechol, m.p. 184° (undepressed when admixed with an authentic sample prepared as described by Zincke and Kuster (7)).

Reaction of (IIa) with phenylhydrazine.—The cyclic ether (1 g) and phenylhydrazine (1 g) in absolute ethanol (20 ml) were refluxed together for 3 hours. The solution was filtered while hot, concentrated, and left to cool. The solid formed was filtered off and recrystallized from ethanol to give golden yellow crystals, m.p. 152 °C (0.5 g), which proved to be xanthone phenylhydrazone (m.p. and mixed m.p.). Tetrachlorocatechol was produced in the reaction and identified as before.

Reaction of (IIa) with benzoylhydrazine.—The reaction was carried out as above using half a gram of the ether and one-fifth of a gram of the hydrazine. The solution was cooled and the yellow solid formed was crystallized from benzene to give xanthone benzoylhydrazone as yellow crystals, m.p. 150 °C. Calc. for $C_{20}H_{14}O_2N_2$: C, 76.43; H, 4.46; N, 8.91. Found: C, 77.00; H, 4.65; N, 8.66%.

Reaction of (IIa) with xanthone hydrazone.—A suspension of (II*a*) (1 g) and the hydrazone (1 g) in absolute alcohol (20 ml) were refluxed together for 5 hours and the mixture was left to cool. The solid formed was crystallized from xylene to give xanthone azine (0.56 g) as orange yellow crystals, m.p. 295 °C (undepressed when admixed with an authentic sample).

Reaction of malononitrile with (IIa).—Malononitrile (0.3 g) was added to a suspension of (II*a*) (1 g) in absolute alcohol (20 ml) and the reaction mixture was refluxed for 4 hours. During this period the cyclic ether went gradually into solution and a yellow crystalline solid was formed. This was filtered off and recrystallized from benzene to give Δ^9,α-xanthenemalononitrile (V*a*) as green yellow crystals (0.35 g), m.p. 244–245 °C (undepressed when admixed with a sample prepared by condensing 9,9-dichloroxanthene with malononitrile (6)). Tetrachlorocatechol was identified in the ethanolic mother liquor as before. When the reaction was carried out using equimolecular amounts of the reactants, almost the same yield of (V*a*) was obtained.

Preparation of 9,9-(tetrachloro-o-phenylenedioxy) thiaxanthene (IIb).—Tetrachloro-*o*-benzoquinone (0.8 g) was added portionwise, at room temperature (25 °C), to a solution of 9-diazothiaxanthene (8) (1 g) in dry ether (20 ml). A vigorous reaction with evolution of gas took place after each addition and the red color of the quinone disappeared. When all the quinone had been added, the product formed was filtered off, washed with acetone, and recrystallized from the same solvent to give (II*b*) as colorless crystals, m.p. 221 °C (undepressed when admixed with an authentic sample prepared by the reaction of 9,9,dichlorothiaxanthene with tetrachlorocatechol (9)). Both products have identical infrared spectra. Calc. for $C_{19}H_8O_2SCl_4$: C, 51.58; H, 1.81; S, 7.24; Cl, 32.12. Found: C, 51.75; H, 1.99; S, 7.16; Cl, 31.59%.

Preparation of 9,9-(tetrabromo-o-phenylenedioxy) thiaxanthene (IIc).—The reaction was carried out as in the case of the chloro-analogue when (II*c*) was obtained as colorless crystals, m.p. 245 °C (undepressed when admixed with an authentic sample prepared by the reaction of tetrabromo-*o*-benzoquinone with thiaxanthone hydrazone (9)).

Reaction of (IIb) with lithium aluminum hydride.—One gram of (II*b*) was added in small portions to a suspension of lithium aluminum hydride (1 g) in dry ether (40 ml). When all the cyclic ether had been added, the reaction mixture was refluxed for 6 hours on the water bath, and left to cool. It was decomposed with alcohol then with dilute hydrochloric acid, and extracted several times with ether. The combined ethereal extracts were dried over anhydrous sodium sulphate, and the ether was then driven off. The solid left was dissolved in the least amount of boiling methanol and the solution was filtered while hot and left to cool. The separated colorless crystals were shown to be thiaxanthene (m.p. and mixed m.p.). The alcoholic mother liquor was poured onto ice-cold water and acidified with a few drops of hydrochloric acid. The precipitate formed was shown to be tetrachlorocatechol as before.

Reaction of hydrazine hydrate with (IIb).—Hydrazine hydrate (99–100%—0.5 ml) and (II*b*) (0.5 g) in absolute alcohol (20 ml) were refluxed together for 3 hours. The reaction mixture was filtered while hot, and the solid obtained (0.002 g) was shown to be thiaxanthone azine (m.p. and mixed m.p.). The filtrate was concentrated and cooled. The pale yellow solid formed (0.16 g) was filtered off, crystallized from ethanol, and shown to be thiaxanthone hydrazone (m.p. and mixed m.p.). Tetrachlorocatechol was identified in the main alcoholic mother liquor as before.

Reaction of phenylhydrazine with (IIb).—The reaction was carried out as above using half a gram of phenylhydrazine and half a gram of (II*b*). The solution was filtered while hot, concentrated, and left to cool. The crystalline solid formed (0.31 g) was filtered off, and recrystallized from methanol to give thiaxanthone phenylhydrazone as yellow crystals, m.p. 150–151 °C. It gives an olive green color with deep green fluorescence with concentrated sulphuric acid. Calc. for $C_{19}H_{14}SN_2$: C, 75.49; H, 4.63; S, 10.59; N, 9.27. Found: C, 75.27; H, 4.83; S, 10.55; N, 9.25%. Tetrachlorocatechol was produced in the reaction and identified as above.

Reaction of benzoylhydrazine with (IIb).—The reaction was carried out as above. The solution was filtered while hot and evaporated to dryness under reduced pressure, and a few milliliters of methanol was added to the oily residue. The light yellow solid formed (0.24 g) was filtered off and crystallized from methanol to give thiaxanthone benzoylhydrazone as straw yellow crystals, m.p. 177 °C. Calc. for $C_{20}H_{13}OSN_2$: S, 9.72; N, 8.51. Found: S, 10.41; N, 8.36%. Tetrachlorocatechol was identified in the alcoholic mother liquor as above.

Reaction of malononitrile with (IIb).—Malononitrile (0.5 g) and the cyclic ether (II*b*) (0.5 g) in absolute alcohol (30 ml) were refluxed together for 6 hours. The orange yellow crystalline solid formed during the reaction was filtered off, washed with acetone, and crystallized from benzene to give Δ^9,α-thiaxanthenemalononitrile (V*b*) (0.2 g) as orange yellow crystals, m.p. 300–301 °C (undepressed when admixed with an authentic sample prepared by the reaction of 9,9-dichlorothiaxanthene with malononitrile (6)). Tetrachlorocatechol was produced in the reaction and identified as above.

Reaction of ethyl cyanoacetate with (IIb).—A mixture of (II*b*) (1 g) and ethyl cyanoacetate (1 ml) in *n*-butyl alcohol (20 ml) was refluxed for 6 hours. The solution was filtered while hot, evaporated to dryness under reduced pressure, and a few milliliters of methanol was added to the oily residue. The yellow crystalline solid formed (0.35 g) was filtered off, washed with methanol, and crystallized from the same solvent to give Δ^9,α-thiaxantheneacetic acid, α-cyanoethyl ester (V*c*) as yellow crystals, m.p. 129–130 °C (undepressed when admixed with an authentic sample prepared by the reaction of 9,9-dichlorothiaxanthene with ethyl cyanoacetate (6)). Tetrachlorocatechol was identified in the main methanolic mother liquor as before.

Reaction of malononitrile with dixanthenyl ether.—To a suspension of dixanthenyl ether (1.8 g) in absolute alcohol (25 ml), malononitrile (0.6 g) was added, and the reaction mixture was refluxed for 4 hours. During this period the ether went gradually into solution and a crystalline solid was formed. This was filtered off, and the filtrate was concentrated, and left to cool. The solid separated was filtered off, and crystallized from ethanol to give 9-xanthyl malononitrile (VIII*c*) (1.1 g) as colorless crystals, m.p. 186–188 °C (undepressed when admixed with an authentic sample prepared by the reaction of xanthydrol with malononitrile (10)).

Reaction of ethyl cyanoacetate with dixanthenyl ether.—Ethyl cyanoacetate (2.5 g) and dixanthenyl ether (3.7 g) in absolute alcohol (25 ml) were refluxed together for 6 hours. The solution was filtered while hot, and evaporated to dryness. The oily residue obtained was extracted several times with cold petroleum ether (b.p. 40–60°). The solid obtained (1.4 g) was filtered off, washed with methanol, and crystallized from ethanol to give (VIII*b*) (11) as colorless crystals, m.p. 125–127 °C. Calc. for $C_{18}H_{15}O_3N$: C, 73.72; H, 5.11; N, 4.77. Found: C, 74.04; H, 4.97; N, 4.22%.

Reaction of benzoylhydrazine with dixanthenyl ether.—The reaction was carried out as above using 0.8 g of benzoylhydrazine and 1.8 g of the ether. The solution was filtered off, concentrated, and left to cool. The solid separated was filtered off, and crystallized from ethanol to give (VIII*a*) (12) as colorless crystals, m.p. 176–178 °C (yield 1.7 g). Calc. for $C_{20}H_{16}O_2N_2$: C, 75.94; H, 5.10; N, 8.86. Found: C, 75.52; H, 5.37; N, 8.98%.

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