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SMILES REARRANGEMENTS IN THE SYNTHESIS OF HEXACHLORODIBENZO-p-DIOXINS[1]

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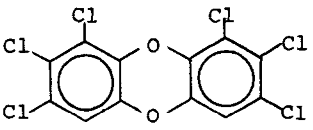
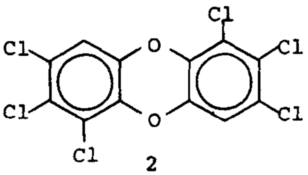
Chlorinated dibenzo-p-dioxins pose a severe environmental hazard because of their extreme toxicity and persistence in the ecosystem.[3] The compounds 1,2,3,7,8,9-hexachlorodibenzo-p-dioxin **1** and 1,2,3,6,7,8-hexachlorodibenzo-p-dioxin **2** have been directly implicated in the death of millions of young chickens (chick edema).[4] As part of our continuing program of synthesis, characterization, and biological evaluation of toxic polychlorinated aromatics,[5] we undertook regiospecific syntheses of hexachlorodioxins **1** and **2**. Since conventional techniques for the construction of the dibenzo-p-dioxin ring system[5,6] were expected to afford mixtures of regioisomers, a new procedure involving a masked "predioxin" was devised. We chose as the key intermediates functionalized hexachlorodiphenyl ethers in which the location of the requisite chlorines could be controlled by the choice of starting materials.

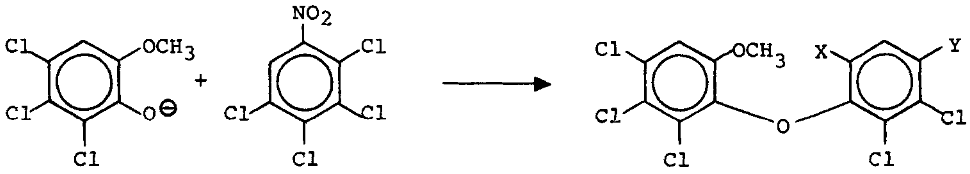


1



2

Reaction of the potassium salt of 4,5,6-trichloroguaiacol[7] **3** with three equivalents of 2,3,4,5-tetrachloronitrobenzene in refluxing acetonitrile for five days resulted in clean formation of the two diphenyl ethers **4a** and **4b**. That the condensation had given a ca. 1:1 mixture of these isomers was demonstrated by pmr spectroscopy; the chlorine content was confirmed by mass spectroscopy.[8]

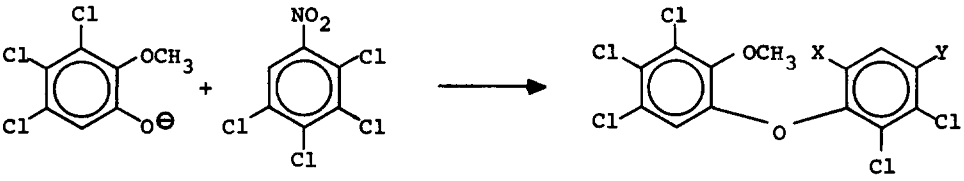


3

4a X = NO_2 Y = Cl

4b X = Cl Y = NO_2

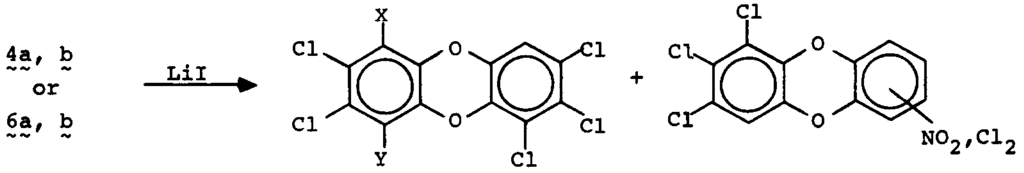
A similar condensation of the potassium salt of the hitherto unknown 3,4,5-trichloroguaiacol[9] 5 with 2,3,4,5-tetrachloronitrobenzene afforded a mixture of two new diphenyl ethers 6a and 6b, characterized as above.[10] It was anticipated that deblocking of 4a followed by intramolecular displacement of *nitrite* would lead to 1 as the exclusive hexachlorodioxin component and that 6a would likewise provide only 2.



5

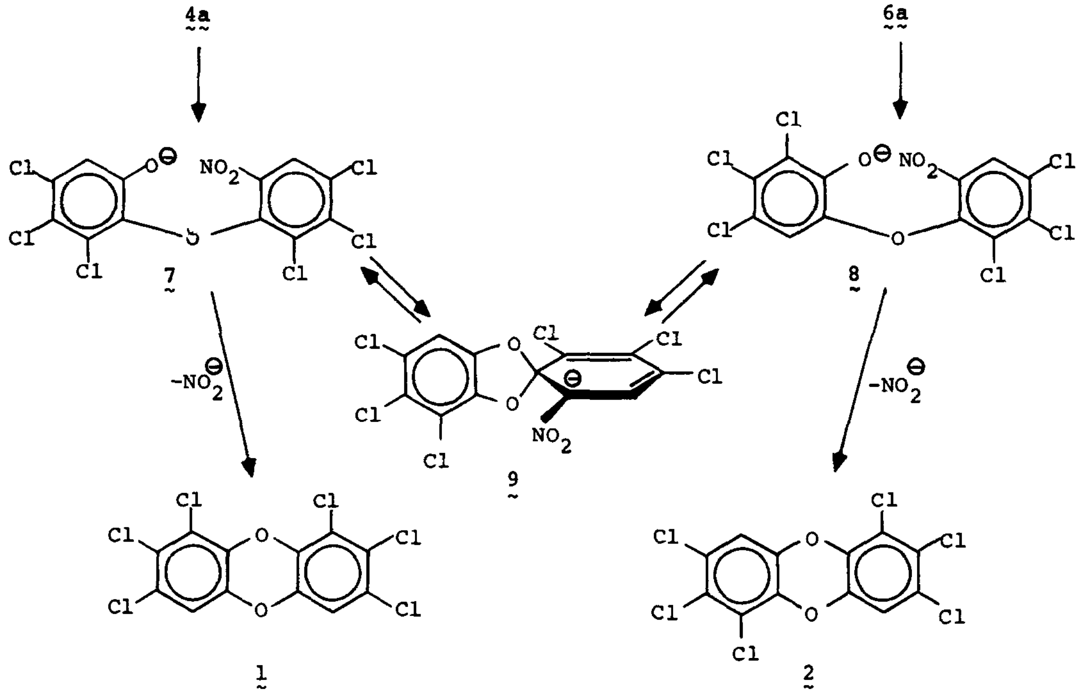
6a $X = NO_2$ $Y = Cl$
6b $X = Cl$ $Y = NO_2$

Treatment of the inseparable mixture of 4a and 4b with four equivalents of lithium iodide in refluxing dimethyl sulfoxide or dimethylformamide effected both quantitative removal of the phenol protecting group[11] and subsequent intramolecular cyclization of the resulting predioxin. The hexachlorodioxin fraction was separated from various uncharacterized nitropentachlorodioxins by thin layer chromatography (SiO_2, 1:1 hexane-benzene). Surprisingly this material was found to be a *ca.* 2.5:1 mixture of two isomeric hexachlorodioxins on the basis of glc analysis[12] [retention times relative to dieldrin 1.99 (2.5), 1.95 (1)], pmr data [in $CDCl_3$: δ6.98, s(2.5); δ7.10, s(1)] and mass spectrum (pattern for Cl_6 having major peak at m/e = 390). In a similar manner, LiI treatment of the 6a and 6b mixture resulted in the identical ratio of the same two hexachlorodioxins as determined by glc, pmr, and ms criteria. In view of the pmr singlet for each component and their relative retention times[4] these hexachlorodioxin isomers were presumed to be structures 1 and 2 respectively. The identities of the major and minor product were so established by comparison with authentic samples isolated by Gray and Cepa for which the structures had been confirmed by Cantrell through single crystal X-ray analysis.[13]



1 X = H Y = Cl
2 X = Cl Y = H

The formation of both hexachlorodioxin isomers in the same ratio from either precursor 4a or 6a suggests rapid interconversion of the two phenoxides 7 and 8 prior to dioxin formation. The delocalized spirocyclic anion 9 depicted in the scheme below provides a convenient intermediate for this equilibration and is of the type found in the well-documented Smiles rearrangement.[14] To our knowledge this is the first demonstration of a Smiles rearrangement in the synthesis of a dibenzo-p-dioxin, although Drozd and coworkers have isolated a related spirocyclic complex and have shown that it is converted to the dioxin skeleton upon standing in dimethyl sulfoxide.[15] We propose that Smiles rearrangements are far more prevalent in the dioxin ring system than heretofore suspected and may account for the formation of unexpected products in syntheses in the dibenzo-p-dioxin and thianthrene series.[16,17]



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1. Support of this work through NIH Grant 5R01 ES00965 is gratefully acknowledged.
2. National Institutes of Health Postdoctoral Fellow, 1973-75.
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8. Pmr ($CDCl_3$): δ7.92, 7.83 (1H); 6.92, 6.88 (1H); 3.66, 3.60 (3H). Ms (20 eV): m/e 449(53), 451(100), 453(83), 455(37), 457(10), 459(1.5). All new compounds gave satisfactory elemental analyses.
9. Mp. 86.8-87.4°; pmr ($CDCl_3$): δ7.04 (1H), 5.7 (1H), 3.90 (3H). Prepared from 2,3,4-trichloroanisole by a sequence of nitration, reduction and hydrolysis of the diazonium fluoborate. *cf.*: A. H. Lewin and T. Cohen, *J. Org. Chem.*, **32**, 3844 (1967).
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