Tetrahedron Letters No. 33, pp 2873 - 2876, 1975. Pergamon Press. Printed in Great Britain.

INTERVENTION OF THE SMILES REARRANGEMENT IN SYNTHESES OF DIBENZO-*P*-DIOXINS. 1,2,3,6,7,8- AND 1,2,3,7,8,9-HEXACHLORODIBENZO-*P*-DIOXIN (HCDD)

Allan P. Gray,* Steven P. Cepa and Joseph S. Cantrell[1]

Chemistry Research Division, IIT Research Institute

Chicago, Illinois 60616

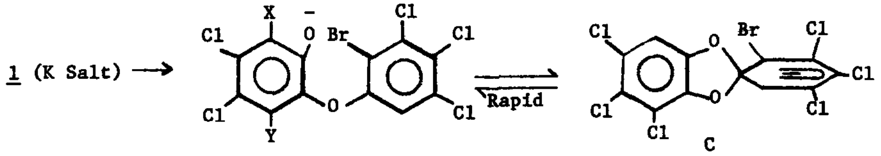
(Received in USA 27 May 1975; received in UK for publication 7 July 1975)

CAUTION CERTAIN POLYCHLORODIBENZO-*P*-DIOXINS HAVE BEEN FOUND TO BE HIGHLY TOXIC AND SHOULD BE HANDLED WITH EXTREME CARE. WORK WAS CARRIED OUT IN GLOVE BOXES IN A TOXIC LABORATORY FACILITY EXHAUST AIR WAS FILTERED ALL WASTES WERE INCINCERATED. CONTACT WITH THESE COMPOUNDS CAN CAUSE CHLORACNE AND IRREVERSIBLE LIVER DAMAGE

The identification of certain polychlorodibenzo-*p*-dioxins, notably the 2,3,7,8-tetrachloro-[2] (TCDD) and 1,2,3,7,8,9-HCDD[3] (3) derivatives as environmental contaminants and the realization of their high mammalian toxicity has aroused concern and prompted investigation of these materials. A number of polychloro- (particularly through tetrachloro) dibenzodioxins have been prepared by the Ullmann copper-catalyzed self-condensation of the appropriate potassium phenolates[4,5] and/or by catechol condensation reactions.[5,6] Attempts to prepare HCDD isomers in pure form by parallel methods have, however, thus far been largely abortive.[4,5]

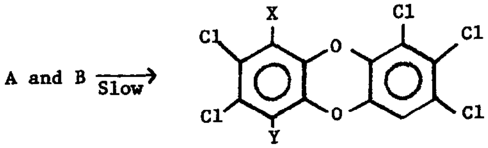
In the course of an investigation directed toward synthesis of a number of polychlorinated dibenzodioxins,[7] we have now found that both condensation reactions proceed *via* Smiles rearrangement [8] Evidence suggests that a Smiles rearrangement intermediate always intervenes in these processes and that the proportion of isomers formed may be product controlled

Thus, self-condensation of the potassium salt of 2-bromo-3,4,5-trichlorophenol (1) followed by selective lithium aluminum hydride (LAH) debromination of bromo-chlorodibenzodioxin contaminants afforded two isomeric HCDD products in a 28 72 ratio (glc). The two products have been isolated by procedures described in the following X-ray analysis of the two isomers has established the predominant product to be 3, which must arise *via* Smiles rearrangement, and the minor component to be 1,2,3,6,7,8-HCDD (2), the expected product of the reaction. The reaction is presumed to take the following course·



A, X=H,Y=Cl

B, X=Cl,Y=H



2, X=H,Y=Cl

3, X=Cl,Y=H

The initially formed anion A rapidly equilibrates through C with the rearranged anion B. In a slow process, A cyclizes to the expected product 2 and B to the rearranged isomer 3.

In parallel work which is being communicated simultaneously, Kende and DeCamp[9] have carried out related condensations of catechol derivatives with nitropolychlorobenzenes and have sent samples of their product mixtures to us for glc analysis. Irrespective of whether the product of direct condensation was expected to be 2 or 3, the two isomers were formed in roughly the same proportion we observed, with 3 predominating.

Since these dibenzodioxins are apparently formed as by-products of the manufacture of polychlorophenols, present results explain how 3 could have arisen as an environmental contaminant,[3, 10] a fact which had remained perplexing. Other previously unexplained findings[11, 12] clearly are also rationalized in terms of the Smiles rearrangement. It may be noted that formation of 2,3,7,8-TCDD, an appropriately symmetrical molecule, will take place in condensation reactions regardless of whether or not rearrangement is involved.

Initial attempts to effect self-condensation of potassium 2,3,4,5-tetrachloro- and of 6-bromo-2,3,4-trichlorophenolate[4,13] having afforded low yields of complex mixtures, we began to examine the possible use of 1. Dropwise addition of one equivalent of bromine to an aqueous acetic acid solution of 3,4,5-trichlorophenol gave a product mixture containing 30-50% of 2,6-dibromo-3,4,5-trichlorophenol (4) and considerable starting material. When, however, the bromine was added all at once to a hot (80-90°), solution of the phenol in glacial acetic acid, 1 was obtained in a yield after recrystallization (methanol-water or benzene-haxane) of 79%, mp 101.3-101.9°, containing (glc) 2.5% starting material and 3.5% 4: calcd for $C_6H_2BrCl_3O$ C, 26.03; H, 0.73; found: C, 26.25; H, 0.78. Addition of 2 equivalents of bromine gave 4, mp 175-178°, 91% pure (glc).

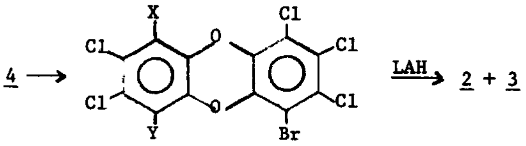
Self-condensation of the K salt of 1 was tried under a variety of conditions. Most convenient and effective was found to be heating the dry salt in a vacuum sublimator essentially as described by Pohland and Yang[5] except that, at least with the o-bromophenolates, a Cu catalyst proved unnecessary, reactions without Cu simply requiring slightly higher (ca. 20°) temperatures.[7] Regardless of the conditions, 2 and 3 invariably formed in roughly a 1:2.5 ratio.

Finely powdered 1 K salt, 11.25 g (0.036 mol), was placed in a vacuum sublimation apparatus, covered with a layer of K_2CO_3,[14] and heated without Cu catalyst at a bath temperature of 245-260° (or at 220-230° in the presence of Ullmann Cu) for 21 hr at 0.7 mm. The sublimed product was rinsed off the cold finger with $CHCl_3$ and the solvent evaporated to yield 1.47 g (21%) of material indicated (glc-mass spectral analysis) to contain 69.5% of 2 and 3 in a ratio of 28.3:71.7, 27.4% of monobromohexachlorodibenzodioxins (from reaction of 1 with the dibromo contaminant) and small amounts of other impurities.

A dry tetrahydrofuran solution, cooled to 2±1°, of 3.3 g of alkali-washed crude product from several runs was treated with LAH added in small portions over 2.5 hr and the reaction was followed by glc. When debromination appeared complete, ethyl acetate and 10% hydrochloric acid were added. A chloroform extract of the reaction mixture deposited a total of 2.4 g of crystals indicated (glc-mass spectral analysis) to contain >95% of 2 and and 3 in about the same 1:2.5 ratio, the balance made up of pentachlorodibenzodioxin isomers (from over-reduction). Repeated recrystallization of material produced in this way, from anisole and from chloroform, afforded 3, 98.8% pure (glc); mp 243-244°; pmr ($CDCl_3$) δ 6.99 (s), mass spectrum (70 eV) 396(10), 394(38), 392(83), 390(100), 388(49), 355(6), 329(14), 327(21), 325(14), 266(8), 264(13), 262(12), 195(13); ir[15] ($CHCl_3$) 3020 (CH stretch), 1570, 1453, 1401 (aromatic stretch), 942 (C-O stretch), 880 (isolated aromatic CH bend), 855 (C-Cl stretch); UVmax ($CHCl_3$) 317 nm (ε = 4070); glc[16] (Dexsil 300) R_{RT} 1.99 (Dieldrin), glc (Apolar 10C) RT 19 6 min; calcd for $C_{12}H_2Cl_6O_2$: C, 36.87; H, 0.52, Cl, 54.42 found: C, 37.16; H, 0.39, Cl, 54.39.

On the hypothesis that product control of the condensation might result in a different isomer ratio from 4, the K salt of 4, 43.8 (0.11 mol), mixed with K_2CO_3 and 2.5 g Cu(Zn) catalyst, was similarly heated in two batches at 265° (bath temp) for 23 hr at 7 mm to yield 5 13 g (16.8%) of material which was indicated (glc) to contain 34.8% of one and 56.6% of another dibromohexachlorodibenzodioxin. This was extracted with 400 ml hot THF. LAH debromination of the dissolved fraction afforded a crude product indicated (glc) to contain 58% 2 and only 8% 3, but which also contained other contaminants that made it difficult to purify. The material which did not dissolve (about half) was dissolved in a mixture of 400 ml of xylene and 200ml of THF. Treatment of the solution with LAH at room temp and workup gave an organic layer which deposited 230 mg of crystals indicated (glc) to be 92 4% 2. The mother liquor contained 2 and 3 in a 1:1 ratio. Recrystallization from chloroform and from anisole gave 2, 98.3% pure (glc); mp 285-286°; pmr ($CDCl_3$) δ 7.11 (s), mass spectrum (70 eV) 396(11), 394(34), 392(84), 390(100), 388(53), 357(8), 355(8), 331(14), 329(12), 327(23), 325(12), 266(6), 264(12), 262(8), 195(9), 194(4), 193(7); UV_{max} ($CHCl_3$) 316 nm (ε = 5950); glc[16] (Dexsil 300) R_{RT} 1.95 (Dieldrin); glc (Apolar 10C) 16 3 min;

found. C, 37.08; H, 0.26, Cl, 54.43.



5, X=Br,Y=Cl
6, X=Cl,Y=Br

The structural assignments for 2 and 3 are supported by X-ray powder analyses, which were carried out on both compounds and which are in accord with theoretical calculations. The powder pattern of 2 differs from, and that of 3 is in good agreement with (in d-spacing and intensity for all low angle lines), the pattern generated (Gandolfi camera) by a single crystal of the isolated chick edema factor previously determined by complete X-ray analysis to be the 1,2,3,7,8,9-isomer.[3]

Acknowledgments: This work was generously supported by FDA Contract No. FDA-223-73-2197 and in part by NCI Contract No. N01-CP-12338. We thank Drs. A E. Pohland, D. Firestone, A.S. Kende and R. H. Stehl for helpful discussions and Drs Kende and DeCamp for supplying some of their materials for analysis. We thank Miss A. D. O'Donnell for the mass spectral data

REFERENCES.

1 Department of Chemistry, Miami University, Oxford, Ohio.

2 For review, see "Chlorodioxins, Origin and Fate," E. H. Blair, Ed., Advances in Chemistry Series, No. 120, A.C.S., Washington, D.C. (1973)

3 J. S. Cantrell, N C. Webb and A. J. Mabis, Acta Crystallogr., B25, 150 (1969).

4. O. Aniline, Ref. 2, p. 126

5. A E Pohland and G. C Yang, J. Agr. Food Chem., 20, 1093 (1972)

6. A. S Kende, J. J. Wade, M. DeCamp, D. Ridge and A. Poland, J. Org Chem., 39, 931 (1974).

7. A complete manuscript also describing other aspects of our work is in preparation

8. W. E. Truce, E. M. Kreider and W W. Brand, Organic Reactions, 18, 99 (1970)

9. A S Kende and M. R. DeCamp, Tetrahedron Letters, 0000 (1975)

10. J C. Wootton and W L. Courchene, J. Agr. Food Chem., 12, 94 (1964)

11. F. P Boer and P. P. North, Acta Crystallogr , B28, 1613 (1972).

12 F P Boer, M. A. Neuman and O. Aniline, ibid., 2878.

13. D. L. Fox and E. E. Turner, J Chem Soc , 1863 (1930).

14 Apparently needed to aid heat transfer, sodium chloride also worked

15. Cf , J -Y T Chen, J.O A.C., 56, 962 (1973)

16. 2 m x 0 32 cm columns, He flow rate 40 ml/min, program (Dexsil 300) 150-295° @ 8°/min, (Apolar 10C) 150-230° @ 10°/min, H_2 fid.