Nitrations of Acylamino- and Nitrodibenzo-*p*-dioxins

James E. Oliver

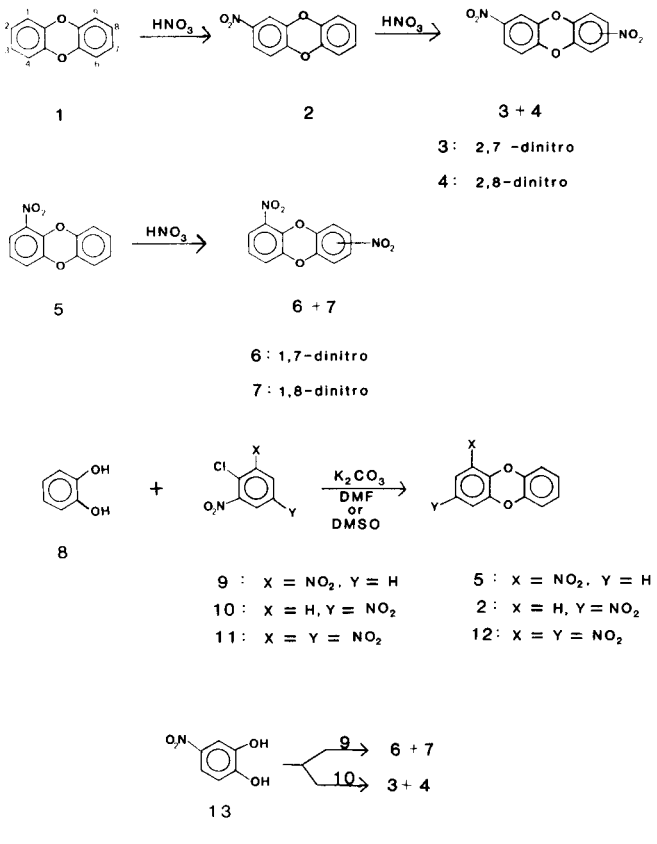
Pesticide Degradation Laboratory, Agricultural Environmental Quality Institute,
ARS, BARC, Beltsville, Maryland 20705

Received January 16, 1984

Nitrations of 1- or 2-acylamino (and nitro) dibenzo-*p*-dioxins were employed to achieve regioselective further functionalization of these compounds. The choice of nitrating conditions and/or acyl substituent (CH_3CO *vs.* CF_3CO) often dictated into which ring the first nitro goroup was directed. In almost all cases, nitrations at the 2,3,7,8-positions were highly favored over nitrations at the 1,4,6,9-positions; with ammonium nitrate/trifluoroacetic anhydride in tetrahydrofuran, however, nitration of 1-(trifluoroacetylamino)dibenzo-*p*-dioxin proceeded predominantly at the 4-position.

J. Heterocyclic Chem., **21**, 1073 (1984).

Chlorinated dibenzo-*p*-dioxins (DD's) have been a subject of intense interest for a number of years. Although much of the attention has been focused on the highly toxic 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (2,3,7,8-TCDD), the suggestions that many of the other polychlorinated DD's may be more commonly occurring than originally supposed [1] have stimulated increased interest in the other chlorinated DD's as well. Many of the chlorinated DD's are not individually available, and although partial characterizations of a number of them have been achieved by application of elaborate analytical techniques to mixtures [2,3,4], the lack of general synthetic methods for selectively preparing unsymmetrically substituted members of the series has become ever more apparent.

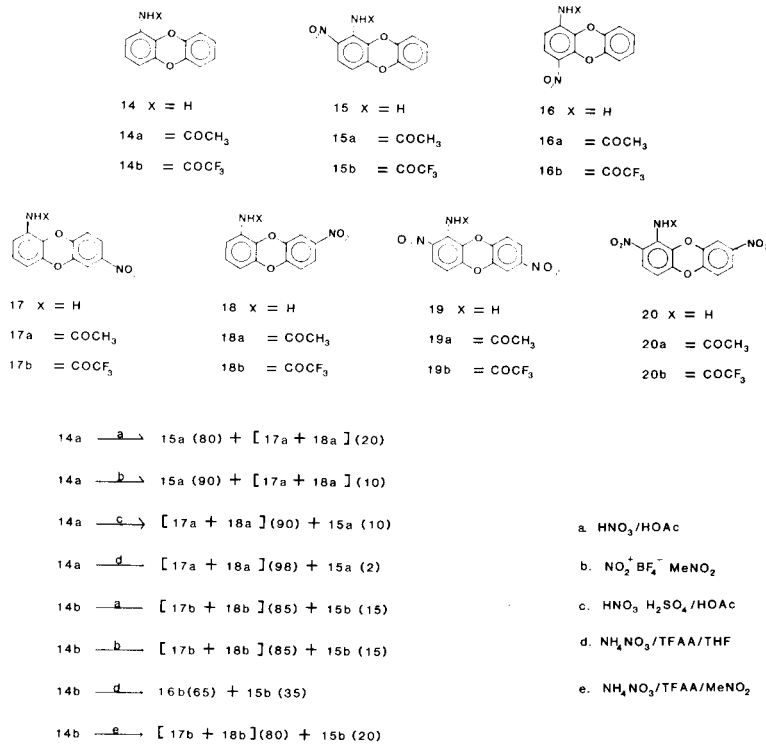


Scheme 1. Mono- and dinitrodibenzo-*p*-dioxins.

The two most common general procedures for preparing DD's are self-condensation of salts of *o*-halophenols and condensation of catechols with polyhalobenzenes or halonitrobenzenes [5]. Both processes are subject to the Smiles rearrangement [6,7] however, and give mixtures of isomers except in selected cases wherein symmetry of at least one of the reactants renders the rearrangement degenerate. Direct halogenations of DD's are of limited utility [8,9].

Nitro DD's have received only limited attention in spite of the potential, *e.g. via* reduction and diazotization, for replacing the nitro groups with other substituents [10,11, 12]. Nitration of the parent compound **1** gives 2-NO_2 DD **2** (Scheme 1); further nitration gives a mixture of the 2,7 and 2,8-dinitro DD's **3** and **4** (which can be separated by fractional crystallization) [10]. Condensation of catechol (**8**) with 2,4-dinitrochlorobenzene (**10**) also gives **2**; with 2,6-dinitrochlorobenzene **9** it gives 1-NO_2 DD **5** [12], and with picryl chloride (**11**) it provides 1,3-dinitro DD **12** [12] (Scheme 1). 1-Nitro-3,7,8-trichloro DD and 1-nitro-2,3,7,8-tetrachloro DD have been prepared by the catechol condensation method and were reduced to the corresponding 1-amino DD's [13]. It was mentioned [8] that 2,3-dichloro DD was nitrated with nitronium tetrafluoroborate to an unidentified mixture of dinitrodichloro DD's; the same authors [14] have recognized the potential for converting nitro DD's to the corresponding halo compounds, but evidently have not extensively exploited it. We noted that 2,3,7,8-TCDD was stable to nitric acid in acetic acid but was destroyed by fuming nitric acid in concentrated sulfuric acid [15]. We have since observed that TCDD can be mono- or dinitrated with nitronium tetrafluoroborate [16].

In addition to their utility as precursors of other substituents, both nitro and amino groups should also have the function of directing incoming groups during electrophilic substitution reactions, and we report here the results of some nitrations of nitro and acylated amino DD's.



Scheme 2. Nitrations of acyl derivatives of 1-aminodibenzo-*p*-doxin. The numbers in parentheses represent approximate distributions of the respective isomers.

Results.

1- and 2- Nitro DD's **5** and **2** (Scheme 1).

As reported [10], 2-NO_2 DD **2** gave a mixture of 2,7- and 2,8-dinitro DD's **3** and **4** upon nitration (we used nitric acid-acetic anhydride). The isomeric products were not well separated by packed column glc, but were readily separated by rp-hplc. Tomita [10] reported that further nitration provided 2,3,7-trinitro DD.

Nitration of 1-NO_2DD **5** does not seem to have been reported; reaction of **5** with nitric acid-acetic anhydride or with ammonium nitrate/trifluoroacetic anhydride [17] gave mixtures of 1,7- and 1,8-dinitro DD's **6** and **7**. Like **3** and **4**, **6** and **7** were better separated by rp-hplc than by glc.

1-Acylamino DD's.

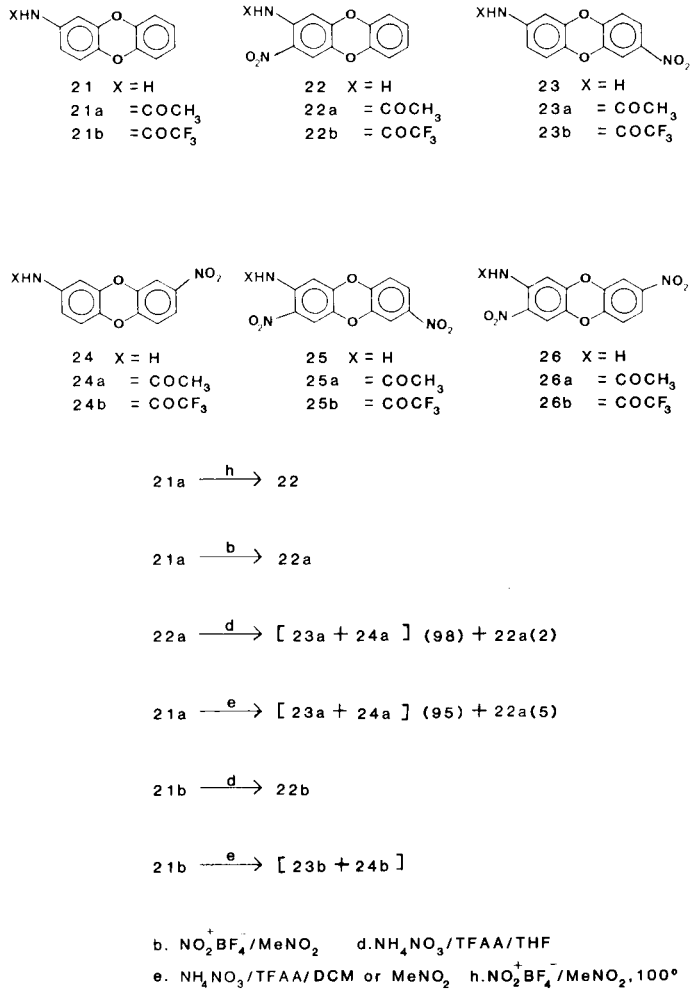
As illustrated in Scheme 2, both the acyl substituent (CH_3CO *vs* CF_3CO) and the nitrating medium influence the position into which the first group is introduced. As expected, the 2,3,7, or 8 positions were substituted in most cases, but in a single case (**14b** and ammonium nitrate-trifluoroacetic anhydride-tetrahydrofuran), nitration occurred predominantly at a *peri*-position. This may be the first example of preferential electrophilic substitution at a *peri*-position in the DD ring system when the 2,3,7,8-positions were available for substitution. From the examples in Scheme 2 it is possible to select synthetically useful conditions for the preparation of **15, 16** or the **17 + 18** mixture. No efforts were made to separate the **17 + 18** mixtures (again better analyzed by hplc than glc), nor were any conditions noted that seem to offer promise toward selectivity forming **17** over **18** or *vice versa.*

2-Acylamino DD's.

In general, mononitrations of **21a** and **21b** (Scheme 3) were somewhat more straightforward than those of **14a** and **14b**, tending to form almost exclusively either the 3-nitro derivative (**22a** or **22b**) or else the 7 + 8 nitro isomers (**23a + 24a** or **23b + 24b**). Again, the **23 + 24** isomers were best analyzed by rp-hplc, and no efforts were made to separate them on a preparative scale.

Dinitration.

In most instances, the same reagents used for mononitrations, if used in excess, gave dinitration products. As would be predicted, **14a** and **14b** gave mixtures of 2,7 and 2,8-dinitro DD's **19a + 20a; 19b + 20b** (Scheme 2), and **21a** and **21b** gave the 3,7- and 3,8-dinitro mixtures **25a + 26a** and **25b + 26b** (Scheme 3). One exception was the curious reaction of **21a** with nitronium tetrafluoroborate. At room temperature with one equivalent of nitronium



Scheme 3. Nitrations of acyl derivatives of 2-aminodibenzo-*p*-dioxin. The numbers in parentheses represent apprixamate distributions of the respective isomers.

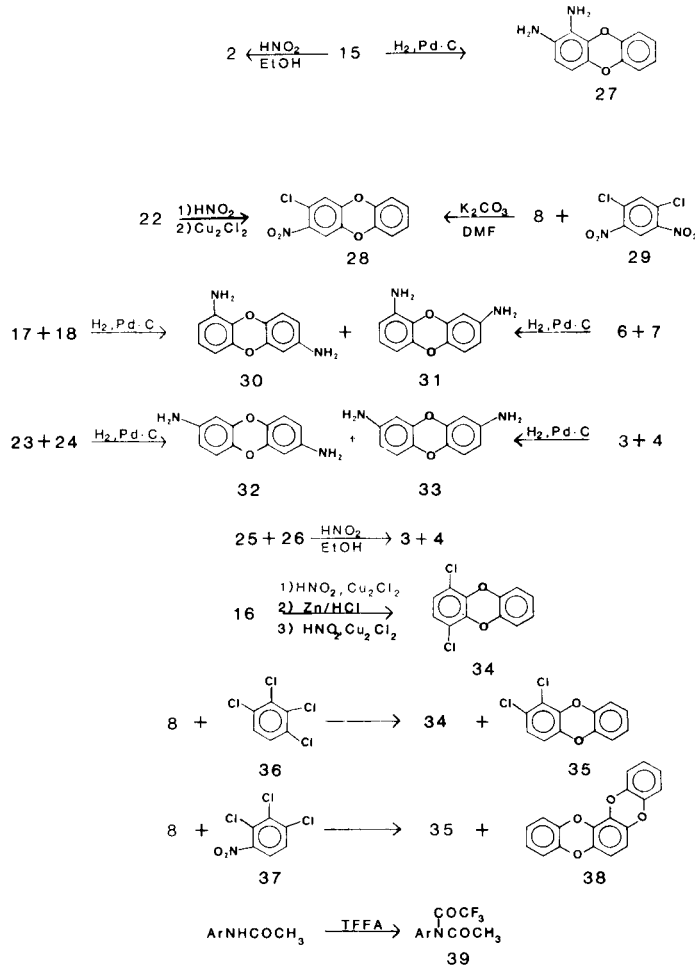
tetrafluoroborate **21a** smoothly gave the 3-nitro derivative **22a**, whereas with two equivalents at 100° the only product identified was the deacetylated 3-mononitro compound **22** (Scheme 3). The other exception was the ammonium nitrate-trifluoroacetic anhydride reagent in tetrahydrofuran. In contrast to the same reagent in nitromethane or dichloromethane, in which cases the stoichiometry of the ammonium nitrate had to be rather carefully controlled to avoid dinitration, the tetrahydrofuran solutions constituted a milder nitrating situation wherein moderate excesses of ammonium nitrate could be used without dinitration becoming a serious problem.

Product Identifications.

Capillary column gas chromatography-mass spectrometry provided empirical formulae of products and in some cases the needed separations to confirm the presence of isomers not well separated by packed column glc. The mass spectra of isomers, however, were very similar to each other and therefore of limited value for positional assignments. Instrumental deficiencies precluded the routine use of nmr spectroscopy, and final structure assignments of nitration products therefore were made on the basis of the chemical conversions described below. All "matches" were based on coelution on both glc and rp-hplc.

2,7- and 2,8-Dinitro DD's **3** and **4**.

These structures were determined by Tomita [10]. Further confirmation resulted from obtaining the same pair of compounds (in almost the same proportions) either by nitrating **2** or by condensing 4-nitrocatechol **13** with 2,4-dinitrochlorobenzene **10** (Scheme 1).



Scheme 4. Chemical transformation used to establish structures of nitrated dibenzo-*p*-dioxins.

1,7- and 1,8-Dinitro DD's **6** and **7**.

Condensation of 4-nitrocatechol **13** with 2,6-dinitrochlorobenzene **9** provided the same mixture of **6** and **7** (again in almost the same proportions) isolated from the nitration of **5** (Scheme 1).

2-Nitro-1-amino DD **15**.

Diazotization/reduction of **15** gave **2**, establishing 2,3,7, or 8 as the position of nitration. Compound **15** was different from either **17** or **18** (7-NO_2-1-NH_2 and 8-NO_2-1-NH_2), leaving only positions 2 and 3. Reduction of the nitro group of **15** (H_2, Pd-C) gave a diamino DD **27**, mp 122-126°, that was different by rp-hplc from the known [10], 1,3-diamino DD, mp 206-207°, prepared by reduction of **12**.

3-Nitro-2-amino DD **22**.

A Sandmeyer reaction (nitrous acid and cuprous chloride) converted **22** to 2-chloro-3-nitro DD **28** that was identical (glc, rp-hplc) to the major product from the condensation of equimolar quantities of catechol and 1,5-dichloro-2,4-dinitrobenzene **29** (Scheme 4).

7-Nitro- and 8-Nitro-1-amino DD's **17** and **18**.

Nitro reduction (hydrogen, Pd-C) of a mixture of **17** and **18** gave the same mixture of diamines **30** and **31** produced upon similar reduction of the **6** and **7** mixture.

7-Nitro and 8-Nitro-2-amino DD's **23** and **24**.

Catalytic reduction (hydrogen, Pd-C) of a mixture of **23** and **24** gave the same mixture of 2,7- and 2,8-diamino DD's **32** and **33** produced by similar reduction of the **3** and **4** mixture (Scheme 1).

3,7- and 3,8-Dinitro-2-amino DD's **25** and **26**.

Diazotization of a mixture of **25** and **26** in ethanol ($ArNH_2 \rightarrow ArN_2^+ \rightarrow ArH$) gave a mixture of **3** and **4**.

2,7- and 2,8-Dinitro-1-amino DD's **19** and **20**.

These structures were assigned from the observation that the same mixtures of **19a + 20a** or **19b + 20b** were formed from dinitration with reagents that gave preferential 2-mononitration as with reagents that gave preferential 7 + 8-mononitration.

4-Nitro-1-amino DD **16**.

Diazotization/reduction of **16** gave **5**, establishing that the NO_2 occupied a *peri* position. A Sandmeyer reaction followed by zinc/hydrochloric acid reduction and a second Sandmeyer reaction converted **16** to 1,4-dichloro DD **34** which was identical to one component of the **34 + 35** mixture resulting from condensation of catechol **8** with 1,2,3,4-tetrachlorobenzene (**36**) [14] (Scheme 4). These results in effect eliminated all other possibilities; however, further confirmation was achieved by an alternative synthesis of **35** (which matched the second dichloro DD of the **8 + 36** product). Condensation of 2,3,4-trichloronitrobenzene **37** with **8** gave **35** along with an unchlorinated product, $C_{18}H_{10}O_4$ to which we assign the pentacyclic structure **38** by analogy to our earlier work [15] (wherein an isomer of **38** was intentionally synthesized by condensation of two equivalents of **8** with **29**).

Discussion.

The results illustrated in Schemes 1-3 show that both nitro and acylamino groups can be used to direct the introduction of one or more nitro groups. In the case of the acylamino derivatives, selection of nitration conditions allows one to dictate to a considerable extent at which position(s) the first nitro group will be introduced into a given substrate. A rather delicate balance seems to exist between preferential nitration of ring A *vs.* ring B; for example, nitration of **14a** with nitric acid in acetic acid gave predominately 2-nitration (a, Scheme 2) whereas nitric acid in acetic acid containing sulfuric acid (c, Scheme 2) resulted in 7 + 8-nitration predominating.

Also worthy of note is the tendency for the CH_3CONH and CF_3CONH groups, under a given set of nitration conditions, to direct the first nitro group to different positions, *e.g.*, a, b, d, Scheme 2; d, Scheme 3. Fukunaga, *et al.* [19] also noted such differences while nitrating acetylamino and trifluoroacetylamino derivatives of biphenyl, fluorene and dibenzofuran, but further noted that the same pairs of derivatives of several anilines and of 1-naphthylamine did not yield different nitration isomers.

Particularly interesting was the effect of THF on the ammonium nitrate-trifluoroacetic anhydride nitrations. This recently introduced nitrating agent (presumably nitronium trifluoroacetate [17]) provides an efficient and mild method for nitration under anhydrous conditions, particularly convenient for aromatic amines because sequential addition of trifluoroacetic anhydride and ammonium nitrate to solutions of the amine achieve both trifluoroacetylation and nitration within 5-15 minutes. Crivello [17] noted that nitrations proceeded faster in polar solvents such as nitromethane, presumably because of a greater solubility of the ammonium nitrate which was added as a solid (to carefully control stoichiometry in small-scale reactions we sometimes found it convenient to use standard solutions of ammonium nitrate to trifluoroacetic acid). Our initial use of tetrahydrofuran as a solvent was fortuitous, simply being based on our experience that most DD's were more soluble in tetrahydrofuran than in nitromethane and on the thought that a water-miscible solvent might facilitate the workup. Nitrations are not traditionally performed in ether solvents, of course; tetrahydrofuran, for example, is known to be oxidized to succinic acid by nitric acid [20] and by dinitrogen tetroxide [21]. Indeed, we found that **14b** was recovered unchanged from treatment with nitronium acetate in tetrahydrofuran (90% nitric acid was added to excess acetic anhydride, and the resulting mixture was added to tetrahydrofuran) and also from nitronium tetrafluoroborate in tetrahydrofuran. Presumably the nitrating agents were consumed by the tetrahydrofuran (but it is not clear why tetrahydrofuran should be more stable to nitronium trifluoroacetate than to nitronium tetrafluoroborate). In the only case examined (nitration of **14a**), substitution of dioxane for tetrahydrofuran gave results identical to those obtained with tetrahydrofuran, suggesting that some property (basicity?) of the ether is responsible for the observed effect.

We have not defined the nature or scope of the solvent effect, or established what factors determine whether a solvent effect will be observed. Substitution of tetrahydrofuran for nitromethane or dichloromethane (the latter solvents gave very similar patterns in the few cases where comparisons were made) resulted in different products with 1-acetylamino DD **14a** and with both 1- and 2-trifluoroacetylamino DD's **14b** and **21b**, but gave the *same* mononitration mixture with 2-acetylamino DD **21a** as well as with 1-nitro DD **5**. Whether the products were the same or different, comparison of the reaction in nitromethane to that in tetrahydrofuran consistently emphasized the greater reactivity in the former solvent. For example, nitration of **5** in tetrahydrofuran at room temperature with a nearly 3-fold excess of ammonium nitrate gave a clean conversion to the pair of dinitro compounds **6** and **7**. When the reaction was repeated in nitromethane with a similar excess of ammonium nitrate, the products were judged (by their long glc retention times) to be at least trinitro DD's, *i.e.*, to represent dinitration. None of either **6** or **7** could be detected. The latter reaction was then repeated with 1.1 equivalents of ammonium nitrate; this time **6** and **7** were cleanly produced in the same approximate ratio as in the tetrahydrofuran reaction.

In the cases of ammonium nitrate-trifluoroacetic anhydride nitrations of the acetylamino DD's **14a** and **21a**,

the actual substrates were probably the mixed bis-acyl derivatives **39**. Both **14a** and **21a** were only sparingly soluble in cold tetrahydrofuran or nitromethane; addition of trifluoroacetic anhydride to suspensions of these compounds, however, produced immediate dissolution of the solids, and gas chromatographic examination showed **14a** and **21a** to have been replaced by earlier-eluting compounds. The nitrated mixed diacyl derivatives were unstable to rp-hplc, chromatographing as the acetyl compounds, but occasionally survived a brief water wash during workup (leading at first to a puzzling discrepancy between glc and hplc analyses and to solutions whose glc traces changed with time). We have not characterized these diacyl derivatives, nor have we seen any evidence of further acylation of the trifluoroacetyl derivatives **14b** and **21b** with either trifluoroacetic anhydride or acetic anhydride. Since the diacyl compounds formed from **14a** and **21a** in either nitromethane or tetrahydrofuran, they do not appear to be particularly relevant to the solvent effects just discussed.

We have at this point illustrated methods for achieving 1,2-, 1,4-, 1,7 + 1,8-, 2,3- and 2,7 + 2,8-di-substitution, as well as 1,2,7(8)- and 2,3,7(8)-trisubstitution, in the DD system, and see no reason why many of the results should not be extendable into chlorinated DD systems and useful for the synthesis of more highly chlorinated DD's.

EXPERIMENTAL [22]

Caution. Just as there is no reason to associate the toxicological properties of 2,3,7,8-tetrachlorodibenzo-*p*-dioxin with the compounds described here, neither is there any justification for assuming that they should be harmless.

Melting points were determined on a Kofler Micro Hot Stage apparatus, or, for compounds that sublimed too rapidly, in sealed capillaries in an oil bath apparatus, and are uncorrected. The glc analyses were performed on a Hewlett Packard 5711A instrument with flame ionization detectors fitted with a 20 inch × 1/8 inch 10% UCW column and with a 6 foot × 1/8 inch 5% silicone fluid QF-1 column. The hplc analyses were performed on Waters instruments equipped with Model 440 UV detectors (254 nm). Most analyses were performed on a Waters 10 cm × 8 mm Radial Pak C18 column eluted with methanol and water; in some cases additional analyses were performed on a 30 cm × 3.9 mm μ Bondapak Phenyl column eluted with acetonitrile and water. Mass spectra were obtained on a Finnigan 4021 spectrometer operated in the electron impact mode (70 eV) fitted with an Incos data system and a 30 m × 0.25 mm id flexible silica capillary glc column coated with SE-30. A few relatively nonvolatile samples were introduced *via* direct probe. Nitromethane was carefully fractionated; THF was distilled daily from potassium hydroxide, and pesticide quality (distilled in glass) dichloromethane was used as received. Nitronium tetrafluoroborate (0.5 *M* in sulfolane) was purchased from Aldrich. Elemental analyses were performed by Galbraith Laboratories, Inc., Knoxville, TN.

1-Aminodibenzo-*p*-dioxin (**14**).

This compound was prepared by catalytic reduction (hydrogen, 10% Pd-C, 50 psi) of an ethanol-THF solution of **5** [12]. Filtration and concentration gave **14** as a light tan solid, mp 126.5-127.5° after recrystallization from heptane.

Anal. Calcd. for $C_{12}H_9NO_2$: C, 72.35; H, 4.55; N, 7.03. Found: C, 72.15; H, 4.88; N, 7.04.

2-Aminodibenzo-*p*-dioxin (**21**).

This compound was prepared from **2**, mp 133-134° (reported [23] mp 134°).

Acetyl and Trifluoroacetyl Derivitaves of 1- and 2-Aminodibenzo-*p*-dioxin **14a, 14b, 21a, 21b**.

These compounds were prepared by treating the respective amines **14** and **21** with a slight excess of acetic anhydride or trifluoroacetic anhydride in dichloromethane or THF.

1-(Acetylamino)dibenzo-*p*-dioxin (**14a**).

This compound had mp 211-213° after recrystallization from acetic acid or acetonitrile.

Anal. Calcd. for $C_{14}H_{11}NO_3$: C, 69.70; H, 4.60; N, 5.81. Found: C, 69.59; H, 4.76; N, 6.04.

1-(Trifluoroacetylamino)dibenzo-*p*-dioxin (**14b**).

This compound was recrystallized from heptane-benzene, mp 198° (sealed capillary).

Anal. Calcd. for $C_{14}H_8F_3NO_3$: C, 56.96; H, 2.73; N, 4.75. Found: C, 56.93; H, 2.99; N, 4.57.

2-(Acetylamino)dibenzo-*p*-dioxin (**21a**).

This compound was recrystallized from acetonitrile, mp 187.5-189°.

Anal. Calcd. for $C_{14}H_{11}NO_3$: C, 69.70; H, 4.60; N, 5.81. Found: C, 69.63; H, 4.70; N, 5.76.

2-(Trifluoroacetylamino)dibenzo-*p*-dioxin (**21b**).

This compound was recrystallized from heptane + benzene, mp 206° (sealed capillary).

Anal. Calcd. for $C_{14}H_8F_3NO_3$: C, 56.96; H, 2.73; N, 4.75. Found: C, 56.87; H, 2.87; N, 4.59.

Nitrations With Ammonium Nitrate/TFAA. Stoichiometric Reactions.

One hundred μl of a 0.083 *M* solution of 1-NH_2DD **14** in trifluoroacetic acid (TFA) was added to 1 ml of dichloromethane, nitromethane or tetrahydrofuran (THF). The solutions were cooled, 50 μl of TFAA was added, and, after a few minutes, 30 μl of 0.33 *M* ammonium nitrate in TFA was added. After 4 minutes, 200 μl of ice water was added and the products were partitioned between DCM and water. The glc analysis indicated two components in the dichloromethane and nitromethane reactions; these were **15b** and the (unseparated) **17b + 18b** pair of isomers in the approximate ratio of 3:7 from the dichloromethane reaction and 2:8 from the nitromethane reaction. Neither starting material nor dinitration products were observed. In contrast, the THF reaction consisted almost entirely of unnitrated **14b**.

Preparative scale reactions in nitromethane or dichloromethane were run similarly (usually 15-30 minutes reaction time) except the substrate was dissolved or suspended directly in the reaction medium and the ammonium nitrate (1.0-1.1 equivalents for mononitrations) was added as a solid. For reactions in THF, 2 or 3 equivalents of ammonium nitrate were used and the reactions mixtures were usually allowed to stir 15-60 minutes at room temperature. In the THF reactions it was often convenient to precipitate the products by addition of water; see, for example, the preparation of **16**.

Other Nitrations.

These were conducted under standard conditions; typical procedures are described in the following examples.

4-Nitro-1-aminodibenzo-*p*-dioxin (**16**).

A solution of **14** (1.0 g, 5 mmoles) in THF (20 ml) was cooled and stirred, then treated with TFAA (5 ml). Within a few minutes a white solid **14b** separated. Solid ammonium nitrate (1 g) was added, the ice bath was removed, and the mixture was stirred 15 minutes at room temperature (a clear amber solution developed). Addition of ice water precipitated a yellow solid (1.72 g) that was crystallized from benzene plus a little heptane to give a mixture of **16b, 15b**, and a small amount of **17b + 18b**.

The mixture was dissolved in methanol (50 ml), a solution of potassium carbonate (5 g) in water (10 ml) was added, and the resulting 2-phase mixture was stirred 18 hours at room temperature, then was filtered to provide a yellow solid that contained some **16** but also contained relatively more of **17** and **18**. Dilution of the filtrate with water gave another crop of material consisting primarily of **16** and **15** (*ca* 7:3); recrystallization from toluene gave 0.148 g of **16** that was ≥95% pure. Evaporation of the mother liquor and crystallization from acetonitrile-water gave 75 mg of essentially pure **15**. An analytical sample of **16** was obtained from another recrystallization from toluene + heptane, mp 168-171° (softening *ca* 158°); ms: 244 ($M^{+\cdot}$) 100%, 214 ($M^{+\cdot}$ -NO) 33%, 198 ($M^{+\cdot}$ -NO_2), 13%, 171, 20%.

Anal. Calcd. for $C_{12}H_8N_2O_4 \cdot H_2O$: C, 54.96; H, 3.84; N, 10.69. Found: C, 55.13; H, 3.17; N, 10.77.

Because of the ambiguity of the preceding elemental analysis, a sample of **16** was converted to its *N*-acetyl derivative, mp (acetic acid) 268-270°; ms: m/e 286 ($M^{+\cdot}$), 100%, 244 ($M^{+\cdot}$ -CH_2CO), 98%, 214 ($M^{+\cdot}$ -CH_2CO-NO), 41%, 198 ($M^{+\cdot}$ CH_2CO-NO_2), 14%.

Anal. Calcd. for $C_{14}H_{10}N_2O_5$: C, 58.71; H, 3.52; N, 9.79. Found: C, 58.51; H, 3.55; N, 9.69.

2-Nitro-1-(acetylamino)dibenzo-*p*-dioxin (**15a**).

A solution of **14a** (370 mg) in acetic acid (10 ml) was cooled and stirred, then treated with a mixture of 1 ml each of acetic acid and 70% nitric acid. A green, then yellow, color developed, and after 5-10 minutes a yellow solid began to separate. A sample taken after 0.5 hour showed considerable unreacted **14a**, and accordingly another mixture of 1 ml of each acetic acid and 70% nitric acid was added. After 15 more minutes at *ca* 10° ice was added, and **15a** (0.36 g) was collected by filtration and purified by recrystallization from acetic acid, mp shrink 238°, 252-257°.

Anal. Calcd. for $C_{14}H_{10}N_2O_5$: C, 58.74; H, 3.52; N, 9.79. Found: C, 58.53; H, 3.77; N, 9.66.

2-Nitro-1-aminodibenzo-*p*-dioxin (**15**).

This compound was prepared by refluxing *ca* 0.3 g of **15a** in a mixture of ethanol (15 ml) and concentrated hydrochloric acid (5 ml) for 6 hours. After standing at room temperature overnight, the mixture was made alkaline with a slight excess of aqueous potassium hydroxide, then was neutralized with acetic acid and **15** (0.2 g) was isolated by filtration and washed well with water. Recrystallization from heptane then from 80:20 acetonitrile-water gave a pure sample, mp 186-188°; ms: m/e 244 ($M^{+\cdot}$), 100%, 214 ($M^{+\cdot}$ -NO), 4%, 198 ($M^{+\cdot}$ -NO_2), 10%, 171 36%.

Anal. Calcd. for $C_{12}H_8N_2O_4$: C, 59.02; H, 3.30; N, 11.47. Found: C, 59.01; H, 3.56; N, 11.39.

3-Nitro-2-(acetylamino)dibenzo-*p*-dioxin (**22a**).

A suspension of 1.33 g of **21a** in 20 ml of nitromethane was cooled and stirred, then 20 ml of 0.5 *M* nitronium tetrafluoroborate in sulfolane was added dropwise. The ice bath was removed, and after stirring at room temperature 1 hour, the nitromethane was removed on a rotary evaporator and addition of water and a little acetic acid promoted the separation of **22a** as a yellow solid. Recrystallization from acetic acid gave a pure sample, mp 230-230.5° (sealed capillary); ms: m/e 286 ($M^{+\cdot}$), 59%, 244 ($M^{+\cdot}$ -CH_2CO), 100%, 240 ($M^{+\cdot}$ -NO_2), 43%, 198 ($M^{+\cdot}$ -CH_2CO-NO_2), 52%, 171, 40%, 43 (CH_3CO^+), 64%.

Anal. Calcd. for $C_{14}H_{10}N_2O_5$: C, 58.74; H, 3.52; N, 9.79. Found: C, 58.61; H, 3.70; N, 9.62.

3-Nitro-2-aminodibenzo-*p*-dioxin (**22**).

Hydrolysis of **22a** with 70% sulfuric acid, *ca* 120° 20 minutes, gave crude **22** that was purified by recrystallization from toluene, mp 216-218° (gradual formation of long red needles during heating).

Anal. Calcd. for $C_{12}H_8N_2O_4$: C, 59.02; H, 3.30; N, 11.47. Found: C, 58.81; H, 3.39; N, 11.36.

2-Chloro-3-nitro DD **28**. A. From **22**.

A solution of **22** (122 mg) in acetic acid (2 ml) and concentrated hydrochloric acid (1 ml) was cooled in an ice bath and treated with a solution of sodium nitrite (100 mg) in water (150 µl). After stirring at 0° 10 minutes a solution of cuprous chloride (400 mg) in concentrated hydrochloric acid (2 ml) was added. The dark mixture was stirred briefly at room temperature then was heated 15 minutes on a steam bath and finally was added to ice. The precipitated tan solid was collected and washed with water (119 mg). It was essentially pure by hplc. Recrystallization from ethanol gave 48 mg of a gold solid, mp 164-166°. An analytical sample was recrystallized from toluene.

Anal. Calcd. for $C_{12}H_6ClNO_4$: C, 54.67; H, 2.29; N, 5.31. Found: C, 54.89; H, 2.45; N, 5.47.

B. From Catechol (**8**) and 2,4-Dichloro-1,5-dinitrobenzene (**29**).

A mixture of **8** (0.775 g) and potassium carbonate (1.05 g) in DMF (13 ml) was stirred and warmed briefly, then 1.67 g (1 eq) of **29** was added and the mixture was refluxed 1.5 hours. After cooling, ice and water were added, the precipitated solid was taken up in toluene and washed with 1*N* sodium hydroxide (a red solid formed that was removed), then water. Concentration gave a yellow solid whose major component (by glc and hplc) was identical to **29** prepared from **22**.

Conversion of **16** to 1,4-Dichloro DD (**34**).

Using the Sandmeyer procedure described for the **22-23** conversion, 4.8 mg of **16** was converted to 4.5 mg 4-nitro-1-chloro DD that was greater than 97% a single component by glc. This material was not characterized; *ca* 4 mg was heated in 1 ml of benzene containing 30 mg of zinc dust and 10 µl aliquots of concentrated hydrochloric acid were added periodically over 1 hour at which time a little more zinc and 2-3 more portions of hydrochloric acid were added. After another 0.5 hour the mixture was partitioned between DCM and aqueous sodium hydroxide. The hplc analysis showed some unreduced 4-nitro-1-chloro DD, so the reduction procedure was repeated. This time reduction was complete, and the product, 4-amino-1-chloro DD, was subjected to another Sandmeyer as described. The product, *ca* 4 mg of a tan solid, was indistinguishable (glc, hplc) from the 1,4-dichloro DD **34** isolated by fractional crystallization from the **34-35** mixture prepared from tetrachlorobenzene **36**.

1,4-Dichloro DD **34** From **8** and **36**.

Catechol (**8**, 0.05 mole) and potassium carbonate (0.1 mole) were combined and briefly warmed in DMF (50 ml), then 0.05 mole 1,2,3,4-tetrachlorobenzene was added and the mixture was refluxed 3.75 hours. Addition of ice precipitated a white solid (odor of tetrachlorobenzene); gc-ms analysis demonstrated a 3-component mixture containing unreacted **36** and two isomeric dichloro DD's **34** + **35**. Two crystallizations from heptane provided a pure sample of the major isomer, mp 149-150°, that was identical (glc, hplc) to **34** prepared from **16**; ms: m/e 252, 254 ($M^{+\cdot}$), 100, 71%, 189, 191 ($M^{+\cdot}$ -COCl), 28, 6%, 126 (M^{++}), 30% [14].

Preparation of 1,2-Dichloro DD **35** From **8** and 1,2,3-Trichloronitrobenzene (**37**).

Catechol (**8**) and **37** were reacted under the conditions described for the **8** + **29** condensation to give a mixture of two components. The earlier-eluting (glc) product proved identical to the minor dichloro DD **35** obtained from **8** and **36**. It was difficult to obtain pure by crystallization because of the lower solubility of the second component; ms: m/e 252, 254 ($M^{+\cdot}$), 100, 69%, 189, 191 ($M^{+\cdot}$ -COCl), 28, 8%, 126 (M^{++}), 32% [14].

Benzo[1,2-*b*:3,4-*b*']bis[1,4]benzodioxin (**38**).

This compound was isolated by fractional crystallization (ethanol + ethyl acetate, then acetonitrile, mp 220-222°) from the **35** + **8** reaction; ms: m/e 290 ($M^{+\cdot}$), 100%, 261 ($M^{+\cdot}$ -HCO), 10%, 205, 11%, 145 (M^{++}), 19%.

Anal. Calcd. for $C_{18}H_{10}O_4$: C, 74.48; H, 3.47. Found; C, 74.23; H, 3.49.

Acknowledgement.

I appreciate the assistance of Dr. John Ruth in obtaining the mass spectra.

REFERENCES AND NOTES

[1] T. J. Nestrick, L. L. Lamparski, L. A. Shadoff, and T. L. Peters in "Human and Environmental Risks of Chlorinated Dioxins and Related Compounds", R. E. Tucker, A. L. Young, and A. P. Grey, eds, Plenum Press, New York, 1983, p 95, and references cited therein.

[2] H. R. Buser and C. Rappe, *Anal. Chem.*, **52**, 2257 (1980).

[3] T. J. Nestrick, L. L. Lamparski, and R. H. Stehl, *Anal. Chem.*, **51**, 2273 (1979).

[4] L. L. Lamparski and T. J. Nestrick, *Chemosphere*, **10**, 3 (1981).

[5] A. P. Grey, S. P. Cepa, I. J. Solomon, and O. Aniline, *J. Org. Chem.*, **41**, 2435 (1976).

[6] A. P. Gray, S. P. Cepa, and J. S. Cantrell, *Tetrahedron Letters*, 2873 (1975).

[7] A. S. Kende and M. DeCampe, *ibid.*, 2877 (1975).

[8] A. S. Kende, J. J. Wade, D. Ridge, and A. Pohland, *J. Org. Chem.*, **39**, 931 (1974).

[9] H. Gilman and J. J. Dietrich, *J. Am. Chem. Soc.*, **79**, 1439 (1957).

[10] M. Tomita, *J. Pharm. Soc. Japan*, **55**, 1060 (1935); *Chem. Abstr.*, **31**, 66614 (1937).

[11] S. Ueo, *Bull. Chem. Soc. Japan*, **16**, 177 (1941).

[12] J. D. Loudon and F. McCaptra, *J. Chem. Soc.*, 1899 (1959).

[13] K. Chae, L. K. Cho, and J. D. McKinney, *J. Agric. Food Chem.*, **25** 1207 (1977).

[14] A. S. Kende and J. J. Wade, *Environ. Health Perspectives*, 49 (1973).

[15] J. E. Oliver and W. R. Lusby, *J. Heterocyclic Chem.*, **15**, 689 (1978).

[16] J. E. Oliver and J. M. Ruth, *Chemosphere*, **12**, 1497 (1983).

[17] J. V. Crivello, *J. Org. Chem.*, **46**, 3056 (1981).

[18] All examples we have seen of electrophilic substitution in the DD system, *eg.* halogenations and nitrations, have occurred preferentially at the 2,3,7 and/or 8-positions (see also ref [8]). The barrier toward further substitution is great enough, for example, to allow 2,3,7,8-tetrachloro DD to be synthesized by direct chlorination of **1**. The difference in reactivity toward nitrations is further emphasized by our observation (described in more detail in reference [16]) that 1,3,6,8-tetrachloro DD is smoothly dinitrated by ammonium nitrate/TFAA/nitromethane at room temperature to 2,7-dinitro-1,3,6-8-tetrachloro DD. Under the same reaction conditions 2,3,7,8-tetrachloro DD was recovered virtually unchanged (*ca* 1-2% conversion to 1-nitro-2,3,7,8-tetrachloro DD, no dinitration).

[19] K. Fukunaga, T. Yoshida, and M. Kimura, *Nippon Kagaku Kaishi*, 133 (1976); *Chem. Abstr.*, **84**, 134794e (1975).

[20] H. Schmid, A. Mashka, and H. Frauenschill, *Monatsh. Chem.*, **80**, 670 (1949).

[21] H. Schmid and A. Mashka, *ibid.*, **80**, 235 (1949).

[22] The mention of firm names or trade products does not imply that they are endorsed or recommended by the U. S. Department of Agriculture over firms or similar products not mentioned.

[23] G. Saint-Ruf and B. Lobert, *Bull. Soc. Chim. France*, 183 (1974).