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Preparation of 1-Ethoxyisobenzofuran. Mechanistic Aspects of the Meerwein Ortho Ester Reaction

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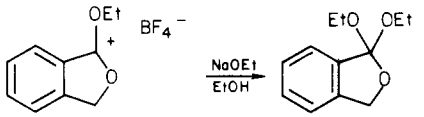
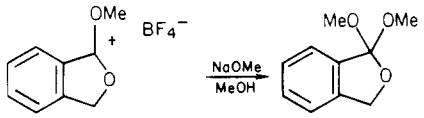
The reaction of *O*-ethylphthalidium tetrafluoroborate (1) with excess $NaOCH_3$ in CH_3OH gives ortho ester 4 as the major product. The mechanism of formation of this solvent-derived material is explored. A plausible intermediate, 1-ethoxyisobenzofuran (8), has been prepared and isolated in solution; 8 reacts readily with, e.g., CH_3OD to give the mixed ortho ester 5 containing ca. one deuterium/mole. This indicates that 8 reacts by rate-determining proton transfer, followed by collapse of the ion pair to give 5. On these and other grounds, 8 is ruled out as an intermediate in the reaction of 1 leading to 4. A mechanism for the latter process consistent with all observations is presented, involving rapid consumption of local alkoxide ion concentration followed by rapid exchange with solvent and eventual neutralization by diffusion of alkoxide from the bulk medium.

One of the standard methods[1] of preparing ortho esters, as introduced by Meerwein,[2] involves the addition of a dialkoxycarbenium tetrafluoroborate to excess sodium alkoxide in alcohol. With lactonium salts, the procedure has been used to prepare ortho esters with two identical alkoxy groups. Thus, *O*-ethylphthalidium salt 1 gives diethyl ortho ester 2 in good yield.[2] Similarly, the methylated salt 3 affords the dimethyl ortho ester[3] 4 on treatment with $NaOCH_3/CH_3OH$.

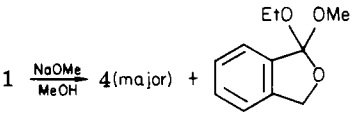


1 2



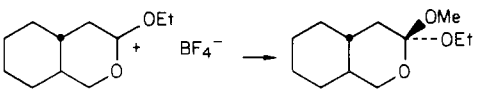
3 4

These reactions would appear to be very simple mechanistically, involving nucleophilic attack by alkoxide on the carbocation center. We were therefore surprised to find that addition of 1 to $NaOCH_3/CH_3OH$ gives as the major product not the mixed ortho ester 5 but instead the solvent-derived material 4, i.e.:



The total yield of ortho ester is essentially quantitative, with 4 accounting for ca. 80% of the mixture. Analogously, addition of 3 to NaOEt/EtOH gave ca. 70% of solvent-derived 2, along with 30% of mixed ortho ester 5. Control experiments established, as expected, that 2 is stable in NaOMe/MeOH and likewise 4 is unaffected by prolonged treatment with NaOEt/EtOH. Therefore, no alkoxy group exchange occurs after the reaction is complete.[4]

A search of the literature revealed that this phenomenon had been observed previously. Deslongchamps,[5] in the course of his elegant studies of stereoelectronic control, required the mixed ortho ester 7. It was noted that when the salt 6 was added to NaOMe/MeOH, the major product



6 7

(1) DeWolfe, R. H. "Carboxylic Orthoacid Derivatives"; Academic Press, New York, 1970.
(2) Meerwein, H.; Borner, P.; Fuchs, O.; Sasse, H. J.; Schrodt, H.; Spille, J. *Chem. Ber.* **1956**, *89*, 2060.
(3) Makhlouf, M. A.; Rickborn, B. *J. Org. Chem.* **1981**, *45*, 2734.
(4) These controls were not carried out in the presence of $NaBF_4$, which precipitates from the carbenium ion salt/alkoxide reactions.[2] It is considered very improbable that this minor difference in conditions would affect the stability of the orthoesters.
(5) Deslongchamps, P.; Chenevert, R.; Taillefer, R. J.; Moreau, C.; Saunders, J. K. *Can. J. Chem.* **1975**, *53*, 1601. See footnote 9 of this reference for another example of this phenomenon and a comment about possible mechanism. The general procedure used in this reference involved addition of a CH_2Cl_2 solution of carbenium ion salt to alkoxide/alcohol at −78 °C, followed by warming to room temperature.

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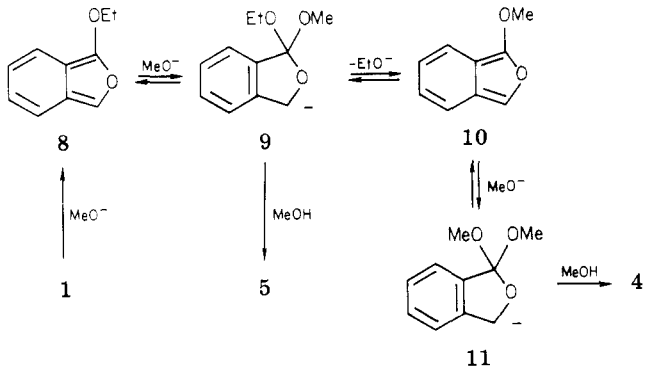
Scheme I



(60%) was the dimethyl ortho ester analogue of **7**, with the remainder (40%) being **7** itself. Interestingly, 97% pure **7** was obtained (76% yield) when **6** was added to NaOMe in 70:30 *i*-PrOH/MeOH mixed solvent.[5]

Deslongchamps' observations coupled with ours suggest that the formation of solvent-derived ortho ester is a general phenomenon and not restricted to a particular substrate structure, e.g., phthalide derivatives, even though different mechanisms might apply.

The original Meerwein procedure for converting **1** to **2** calls for the addition of solid **1** to the alkoxide solution, and this is the method we have typically employed to prepare various ortho esters. With more hydrophobic cations, e.g., the naphthalene analogue of **1**, the reaction is rather slow and apparently controlled by the rate of dissolution of the organic salt in the strongly ionic medium.[6] To examine whether the formation of solvent-derived ortho ester is in some way associated with this two-phase procedure, solutions of **1** in anhydrous acetonitrile were added to rapidly stirred NaOMe/MeOH solutions. While the outcome is affected by this modification, the solvent-derived ortho ester **4** remains the major product. Thus, fairly rapid addition (3 min) of an acetonitrile solution of **1** gave **4**:**5** in a ratio of 65:35, while very slow addition (100 min, syringe pump) led to a 58:42 mixture. Since **4** is formed in solution in these experiments, this seems the most probable pathway also when solid **1** is used.

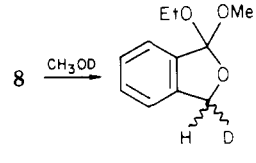
In searching for possible mechanisms for the formation of solvent-derived product, we considered various sites of attack on the cation **1** by methoxide.[7] One might expect **1** to serve as a proton source and react with base to give 1-ethoxyisobenzofuran (**8**), as shown in Scheme I. While such an acid–base reaction seems reasonable and indeed has precedent under different conditions,[3] the formation of **8** does not in itself offer a very attractive way to effect alkoxide exchange. Under basic conditions, this exchange would require rapid and reversible addition of methoxide (alkoxide) to generate carbanions **9** and then **11** via **10**. For formation of **4**, these steps would have to occur more rapidly than protonation of **9** by the methanol solvent to give **5**, and this appeared to be very unlikely. Nonetheless, a simple test of the overall mechanism in Scheme I was available through the use of CH_3OD solvent, and this was carried out. This mechanism requires the incorporation of major amounts of deuterium in the benzylic position of **4**. The reaction gave a mixture of **4**:**5** in a ratio of 81:19, similar to that found in the undeuterated solvent. Integration of the ^1H NMR spectrum indicated that no detectable level of deuterium had been incorporated, and this was confirmed by MS analysis. On this basis it is concluded that **4** is not formed by the route shown in Scheme I.

We were however intrigued by the possible role of **8** in these reactions and continued to examine this question. Extending earlier work on the base-induced 1,4-elimination of the corresponding acetal to form the parent isobenzofuran,[8] it has been shown that the ortho ester **4** can serve as a precursor to 1-methoxyisobenzofuran (**10**) upon treatment with lithium dialkylamide; although we were unable to isolate **10** (in solution, as done with isobenzofuran) under these conditions, its formation was demonstrated by in situ trapping with norbornene.[3] Very recently this procedure has been modified (RLi, catalytic R_2NH) to form relatively uncontaminated solutions of isobenzofuran.[9] This modification has now been applied to the ortho esters **2** and **4**, giving ethereal solutions of **8** and **10**, respectively.[10] These alkoxyisobenzofurans are formed in high yield and exhibit at least moderate stability (0 °C, 0.3 M, no apparent loss over 1 h) when this procedure is used.

Compound **8** is very reactive toward simple hydroxylic solvents, even under basic conditions. An attempt to wash a cold ethereal solution of **8** with 5% aqueous $NaHCO_3$ solution resulted in complete decomposition. When excess methanol was added to a similar solution of **8** (in the presence of precipitated LiOEt) and after a few minutes this mixture was poured into 5% aqueous $NaHCO_3$, mixed ortho ester **5** was obtained in high yield. The same result was found when an aliquot of ethereal **8** was added to excess methanol and also when ethereal **10** was added to ethanol.

Note that this observation establishes that **8** is indeed a viable precursor to ortho ester under neutral/basic conditions, although **8** is *not* an intermediate in the reaction of **1** with NaOMe/MeOH according to the evidence presented above.

The reaction of **8** with methanol is potentially useful and mechanistically interesting. Mixed ortho ester **5** is formed cleanly in this reaction, as judged by NMR and MS. We are aware of only one alternative approach to this material.[11] Some insight into the mechanism of this 1,4-addition was obtained by the use of CH_3OD solvent. Ethereal **8** (7 mL) was added to 5 mL of CH_3OD, and after a short time at 0 °C the aqueous $NaHCO_3$ quench was used. Ortho ester **5**-*d* was obtained in high yield (83% distilled) and shown by ^1H NMR to contain *one* deuterium as illustrated (MS analysis showed 0.90 atom % excess D).



5-*d*

This experiment was repeated but with ethereal **8** added to a solution of NaOMe (5 equiv) in CH_3OD at room temperature. The relatively large amount of ether used

(6) Mir-Mohamad-Sadeghy, B.; Rickborn, B. *J. Org. Chem.* **1983**, *48*, 2237.

(7) In addition to the elimination leading to 1-ethoxyisobenzofuran discussed in the text, one might consider attack by base at the 5-position (para to the cationic center) to give an alternative ketene acetal; while this might occur, it offers no obvious favorable pathway for exchange of alkoxy groups.

(8) Naito, K.; Rickborn, B. *J. Org. Chem.* **1980**, *45*, 4061.

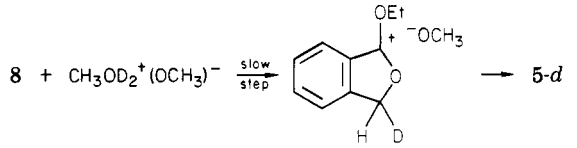
(9) Crump, S. L.; Rickborn, B. *J. Org. Chem.* **1984**, *49*, 304–310.

(10) Further reactions of the alkoxyisobenzofurans, including Diels–Alder applications, are currently being studied.

(11) Hamaguchi, M.; Ibata, T. *Chem. Lett.* **1976**, 287. Copper-catalyzed decomposition of methyl *o*-diazomethylbenzoate in ethanol was reported to give **5** (via **10**), although no supporting evidence for this structure was provided in this brief communication.

caused precipitation of some NaOMe at this stage, and so the effective base concentration is not known. The material balance after workup was again excellent, but the ^1H NMR spectrum of the crude product, in addition to absorptions attributed to **5**-*d*, also exhibited peaks characteristic of phthalide and *ethyl* 2-(hydroxymethyl)benzoate. These last two products are those expected for the reaction of **8** with water, and we believe that their formation indicates the presence of unreacted **8** at the stage of aqueous workup. Thus it appears that methoxide ion does not itself undergo facile reaction with **8** and in fact impedes the reaction of methanol with this substrate. In other words, the addition of alcohol to **8** has the characteristics of an acid-catalyzed process. While not unexpected for a substrate that is formally a ketene acetal, the reaction is unusual in that a 1,4-addition is involved, and it occurs even under fairly basic conditions, no doubt driven by the regeneration of the benzene structure. Isobenzofuran itself does not add methanol at an appreciable rate under similar (neutral) conditions, although cyclic acetal is formed rapidly upon addition of carboxylic acid catalysts. The difference in behavior between **8** and isobenzofuran is rationalized by consideration of the relative stabilities of the carbocation intermediates generated on protonation.

The incorporation of only one deuterium atom in the addition of CH_3OD to **8** when the alcohol is present in large excess shows that the deuterium (proton) transfer step is irreversible and therefore rate determining, as illustrated.

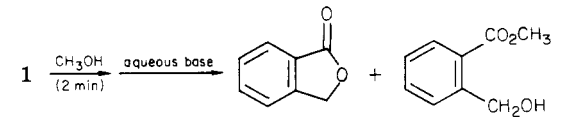


12

This reinforces the earlier conclusion that **1** is not transformed to **8** by NaOMe. The control experiments that established the stability of **2** and **4**, along with the clean formation of **5** when generated in this manner, indicate that the reaction of the cation **12** with methoxide is also effectively irreversible under the neutral/basic conditions employed.[12]

The cation **12** (neglecting D) is identical with **1**, the difference between the two residing in the counterion. Since methoxide ion is also the dominant anion in solution when **1** is treated with excess NaOMe in methanol, the question remains as to why the reaction of **8** with methanol gives only **5**, while **4** is the major product of the procedure starting with **1**, in spite of the apparent common features of both reactions.

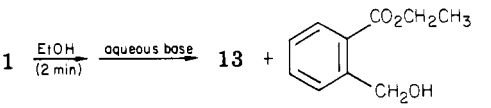
When carbenium ion salts **1** or **3** are simply dissolved in alcohol (no base) and then quenched by addition to aqueous $NaHCO_3$ and ether, the products formed vary with the times involved prior to quench. Thus, when **1** is dissolved in a large excess of methanol and quenched almost immediately (2 min), the products are phthalide (**13**) and the ring-opened ester **14**, in nearly equal amounts, i.e.:



13 **14**

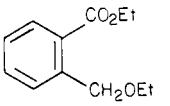
The formation of **14** clearly occurs from some intermediate present at the stage of aqueous quenching (as shown by the formation of hydroxy rather than alkoxy derivative), and presumably most of **13** is formed in this step as well. That the *methyl* ester **14** is formed, starting from the ethylated salt **1**, indicates that a mechanism for rapid exchange exists.

Analogous reaction of **1** in ethanol[13] followed by quenching leads to **13** and the ethyl ester **15** in a ratio of ca. 1:2. The same products are formed in essentially the same amounts if **1** is simply added as a solid to aqueous $NaHCO_3$ solution. When this product mixture is taken up in methanol containing 1 equiv of HBF_4 (commercial acid in ether was used) and then quenched after 2 min, no methyl ester **14** is formed, thus ruling out transesterification of **15** as a source of **14** in the previous experiment.



15

When a solution of **1** in ethanol is allowed to stand (22 °C) for 3.0 h, added to excess NaOMe/MeOH, and then after 3 min poured into aqueous $NaHCO_3$ solution, the major product is phthalide, accompanied by a small amount of material with ^1H NMR absorptions corresponding to **16**. No absorptions for methoxy groups were



16

evident, showing that **1** had reacted completely in the first stage of this sequence.

Taking these several observations into consideration, it appears that the formation of **4** from **1** requires calling upon very fast reactions, the rates of which exceed that of neutralization of acid by diffusion of base from the bulk solvent. Localized zones of lower pH are required to effect "trans-orthoesterification" in order to rationalize the formation of **4** when **1** is added to NaOMe/MeOH. We envisage the process occurring as depicted in Scheme II.

Scheme II

$$1 + NaOCH_3 \rightarrow 5 + NaBF_4 \quad (1)$$

$$1 + CH_3OH \rightleftharpoons 5 + HBF_4 \quad (2)$$

$$5 + HBF_4 \rightleftharpoons 3 + C_2H_5OH \quad (3)$$

$$3 + CH_3OH \rightleftharpoons 4 + HBF_4 \quad (4)$$

$$HBF_4 + NaOCH_3 \rightarrow CH_3OH + NaBF_4 \quad (5)$$

Step 1 represents the undoubtedly fast reaction of **1** with methoxide, consuming the base in proximity to the added salt and leaving only methanol as a nucleophile for further attack of **1**. The equilibria, steps 2–4, must be established

(12) Especially in ether solvent **12** is presumably an ion pair, which might exhibit stereoselectivity in collapse to **5**. The benzylic protons of **5** are not equivalent but exhibit identical chemical shifts at 300 MHz. We plan further work on this interesting question.

(13) The salt **1** dissolves rather slowly in ethanol at ambient temperature, unless a relatively large volume of solvent is used. When this is done (50 mL for 0.8 g of **1**), the quenching step involves competition between water (ca. 30 mL used) and ethanol, and ^1H NMR absorptions characteristic of the ortho ester **2** are seen in addition to those of the products discussed. The dissolution of 0.2 g of **1** in 5.0 mL of ethanol required 25 min (magnetic stirring, 23 °C), during which most of the salt had reacted to give phthalide (83%) and **16** (12%), along with 5% of **15**; the latter reflects the amount of unreacted **1** present at this time.

very rapidly in order to effect alkoxy exchange prior to neutralization of the acid, step 5. While we have made no effort to determine the magnitude of the equilibrium constant for, e.g., step 2, if the carbenium ion salt is strongly favored over ortho ester, combination of steps 2–4 leads to the following limiting case quasiequilibrium:

$$1 + MeOH \rightleftarrows 3 + EtOH$$

While this equation is mechanistically less detailed and informative than the steps in Scheme II, it illustrates the point that significant levels of acidity need not be generated to account for the exchange.

Dioxacarbenium ions such as **1** exhibit a general preference for attack by nucleophiles at the carbocation center, even though more stable products may result from either reversibility of this step or direct attack at alternative sites. McClelland and co-workers have shown,[14] for example, that both the cation and the hemi ortho ester are detectable intermediates in the hydrolysis of **2**. The mechanism for alkoxy group exchange outlined in Scheme II parallels the corresponding stages of the hydrolysis process. Since these rapid reactions are nonetheless not competitive with diffusion-controlled rates for acid–base neutralization, it is clear that the alkoxy group exchange requires nonhomogeneous concentrations of the reactive species, i.e., it is the physical property of rate of mixing which controls the outcome of our reactions. The increased relative amounts of mixed ortho ester **5** associated with efforts to improve mixing efficiency support this view, while also demonstrating that common stirring and slow addition methods are insufficient to overcome completely the fast exchange process. Deslongchamps' observation of improvement in mixed ortho ester formation associated with dilution of the reactive solvent methanol by the less reactive isopropyl alcohol can likewise be rationalized as a mixing phenomenon.

Experimental Section

Ether and acetonitrile were distilled from $LiAlH_4$ and P_2O_5, respectively, immediately before use. Diisopropylamine was distilled from CaH_2 and stored under N_2. Commercial CH_3Li in ether was used. ^1H NMR spectra were recorded on Varian T-60, EM-360, and Nicolet NT-300 instruments, in $CDCl_3$ (Me_4Si standard), unless otherwise stated. MS(EI) and MS–CI (chemically induced, methane flow gas) data were obtained from a VG Micromass ZAB-2F instrument. Meerwein's procedure[2] was used to prepare *O*-ethylphthalidium tetrafluoroborate (1): ^1H NMR (CD_3NO_2) δ 1.7 (t, 3 H), 5.3 (q, 2 H), 6.3 (s, 2 H), 7.7–8.4 (m, 4 H). Dimethyl ortho ester **4** was prepared from **2** as described previously.[3]

***O*-Methylphthalidium Tetrafluoroborate (3).** A mixture of **4** (20.3 g, 0.113 mol) and 100 mL of CH_2Cl_2 (distilled from $LiAlH_4$)[15] was cooled in an ice bath, and 18.5 mL (0.15 mol) of distilled $BF_3{\cdot}Et_2O$ was added by dropping funnel. After stirring for 1 h, the precipitate was isolated by suction filtration under N_2; repeated washing with hexane gave 22.5 g (85%) of colorless crystalline **3**: ^1H NMR (CD_3NO_2) δ 4.8 (s, 3 H), 6.3 (s, 2 H), 7.8–8.35 (m, 4 H).

Reactions of 1 and 3 with NaOR/ROH. Solutions of sodium alkoxide were prepared by adding freshly cut Na to the appropriate alcohol under N_2. Concentrations were varied from approximately 1 to 3 M, and amount of base (per equiv of **1** and **3**) from 1.5 to 3 equiv, with little change in outcome. Most reactions were carried out with ca. 1 g of **1** (or **3**), but much larger scale runs gave essentially identical results. The following examples are representative.

(a) Solid **1** (35 g, 0.14 mol) was added over a few minutes to 300 mL of 3 M NaOMe in MeOH at room temperature; no significant change in temperature was observed.[16] After being stirred for 1 h, the mixture was poured into excess 5% aqueous $NaHCO_3$ solution and ether. The combined ether phase after two further extractions was dried over K_2CO_3 and rotary evaporated to give 20.3 g (ca. 80%) of ortho esters. Analysis of product ratios was done by ^1H NMR integration, measuring the upfield triplet due to $-OCH_2CH_3$ (assigned to mixed ortho ester **5**) and the total integral for absorption in the 3.0–4.0 ppm region, with a cross-check provided by the integral of the benzylic singlet (5.0 ppm) and aromatic protons; no indication of products other than the two ortho esters was present. In this particular reaction, the ratio of **4**:**5** was 74:26.

(b) Solid **3**, 0.50 g, 21 mmol, was added in one portion to 35 mL of 1 M NaOEt in ethanol. The procedure described above was employed, except CH_2Cl_2 solvent was used for extraction. The crude ortho ester mixture (**2**:**5** = 73:27) was obtained in high yield.

(c) A solution of 1.0 g of **1** dissolved in 5 mL of anhydrous acetonitrile was added dropwise over ca. 3 min to a magnetically stirred 1.1 M solution of NaOMe in methanol (30 mL). Workup with ether gave 70% of product, **4**:**5** = 64:36.

(d) A solution of 1.0 g of **1** in 9 mL of acetonitrile was added via syringe pump (1.7 h) to a rapidly (mechanically) stirred solution of 1.0 M NaOMe in 40 mL of methanol. After the usual aqueous base treatment and ether extraction, 76% of product was obtained, **4**:**5** = 58:42.

(e) A solution was prepared by dissolving 0.45 g of Na in 5 mL of CH_3OD, and to this was added 0.70 g of **1**. After being stirred for 0.75 h, the solution was poured into excess 5% $NaHCO_3$ solution and extracted with CH_2Cl_2. Rotary evaporation gave 70% of ortho esters in a ratio **4**:**5** of 81:19. The absence of deuterium in this crude product was established by ^1H NMR integration and by MS, with the latter exhibiting P/(P + 1) ratios for the strong (M – OEt) and M – OMe) peaks characteristic of the normal isotope material.

Alcoholysis/Hydrolysis of 1. (a) Addition of **1** (1.0 g) to rapidly stirred methanol at room temperature followed (after 2 min) by pouring this clear solution into 100 mL of 5% $NaHCO_3$, ether extraction, drying over K_2CO_3, and rotary evaporation gave 0.43 g (71%) of a viscous residue. This mixture showed (only) peaks characteristic of phthalide (**13**) and methyl 2-(hydroxymethyl)benzoate (**14**), with ^1H NMR assignments for the latter being δ 3.90 (s, 3 H), 4.80 (2 H, s on addition of D_2O), 7.3–7.4 (m, 3 H), 7.8–8.1 (m, 1 H). No attempt was made to isolate **14**, which is known[17] to cyclize readily to **13**. The ratio of **13**:**14**, ca. 1:1 in this instance, was determined by integration of the benzylic proton peaks.

(b) An otherwise identical reaction with ethanol in place of methanol gave **13** and ethyl 2-(hydroxymethyl)benzoate (**15**) in a ratio of ca. 1:2, in 85% yield. **15**: ^1H NMR δ 1.40 (t, 3 H), 4.40 (q, 2 H), 4.80 (s, 2 H), 7.3–7.4 (m, 3 H), 7.8–8.1 (m, 1 H).

(c) An essentially identical mixture to that described above (b) was isolated when 1.2 g of **1** was added directly to 50 mL of $NaHCO_3$ solution. This mixture was then taken up in 50 mL of methanol, and 0.5 mL of 50% HBF_4 in ether was added. After being stirred for ca. 2 min at room temperature, the mixture was quenched in the usual way; the proportion of **13** had increased to nearly 50% but no methoxy signals were evident in the NMR of this material, i.e., no transesterification had occurred.

(d) When 1.0 g of **1** was added to 5.0 mL of ethanol at 22 °C, 3 h of stirring was required to obtain a clear solution. At this point the mixture was added to 50 mL of ca. 1 M NaOMe in methanol and stirred for 0.5 h. The usual bicarbonate treatment and ether extraction gave a mixture of **13** and ethyl 2-(ethoxymethyl)benzoate (**16**) in 90% yield, in a ratio 13:16 of 85:15; **16** was isolated by preparative TLC: ^1H NMR δ 1.30 (t, 3 H), 1.45 (t, 3 H), 3.65 (q, 2 H), 4.35 (q, 2 H), 4.90 (s, 2 H), 7.2–8.1 (m, 4 H); MS–CI, *m/z* (relative intensity) 209 (100), 207 (26), 179 (17), 164 (37), 163 (100), 135 (34), 133 (35); calcd for $C_{12}H_{17}O_3$ (P + H) 209.1200; found 209.1189.

(14) McClelland, R. A.; Alibhai, M. *Can. J. Chem.* **1981**, *59*, 1169.
(15) Moss, R. J.; Rickborn, B. *J. Org. Chem.* **1982**, *47*, 5391.
(16) The absence of an exotherm appears to be associated with concurrent precipitation of $NaBF_4$. When LiOMe was used in a small-scale reaction, no precipitate was seen, and the reaction flask became detectably warmer. This change in metal ion had no effect on yield or ratio of products.
(17) Fife, T. H.; Benjamin, B. M. *Bioorg. Chem.* **1976**, *5*, 37.

1,3-Dihydro-1-ethoxy-1-methoxyisobenzofuran (5).[18] A mixture of 0.90 g (4.3 mmol) of **2** and 35 μL (0.21 mmol) of diisopropylamine in 12 mL of anhydrous ether under N_2 was cooled in an ice/salt bath. Methyllithium in ether (3.4 mL, 4.7 mmol) was added by syringe. After stirring for 0.5 h, a sample of the yellow solution, from which LiOEt had precipitated, was removed and examined by ^1H NMR, which indicated complete conversion of **2** to 1-ethoxyisobenzofuran (**8**): δ 6.45–6.90 (m, 2 H), 7.05–7.40 (m, 2 H), 7.45 (s, furan proton). These chemical shifts (in ether) are based on the observation that the broadened singlet aromatic absorption of **2** appears at essentially the same chemical shift in ether, THF, and $CDCl_3$ solvents. Methanol (20 mL) was added to the remaining reaction mixture, with stirring continued for 0.25 h at 0 °C, after which this solution was quenched and extracted in the usual way. Evaporation gave 724 mg of liquid residue, nearly pure **5** by NMR analysis. High-vacuum short-path distillation (60 °C) gave 665 mg (80%) of pure **5** as a colorless oil: ^1H NMR (300 MHz) δ 1.20 (t, 3 H), 3.28 (s, 3 H), 3.43 (dq, J = 9.3, 7.2 Hz, 1 H, diastereotopic -OCH_2CH$_3$), 3.64 (dq, 1 H), 5.09 (s, 2 H), 7.23–7.45 (m, 4 H); MS, m/z (relative intensity) 163 (54), 149 (100), 135 (81), 133 (37), 105 (23), 91 (17), 77 (20); calcd for $C_{10}H_{11}O_2$ (P – OMe) 163.0759; found 163.0769. Calcd for $C_9H_9O_2$ (P – OEt) 149.0602; found 149.0594.

3-Deuterio-1,3-dihydro-1-ethoxy-1-methoxyisobenzofuran (5-*d*). Samples of **5-*d*** were prepared either by addition of an ethereal solution of **8** to a large excess of CH_3OD or by addition of CH_3OD to a solution of **8** that had been filtered to remove precipitated LiOEt, with stirring at 0 °C for ca. 0.5 h prior to the usual workup. Yields are high in both cases; **5-*d*** has NMR characteristics identical with **5**, except for broadening of the benzylic proton due to deuterium coupling and the diminished integral of this peak. MS analysis was accomplished by examination of the appropriate M/(M + 1) ratios for the P – OEt and P – OMe peaks, taking into account ^{13}C contributions. These indicated 89% and 90% deuterium incorporation in the two samples; the m/z 149–151 peaks are the more pertinent for this analysis, since the 163, 164 peaks are affected by any unreacted **2** in the mixture, as observed in one run.

(18) In principle it should be possible to prepare **5** from **1** by using alcohol-free alkoxide in a solvent suitable for both the base and **1**. We have approached this by using LiOMe (prepared in methanol with subsequent vacuum removal of solvent) in acetonitrile, to which **1** was added as a solid. This gave a **4**:**5** ratio of 5:95. Further improvement should be possible by generating LiOR from stoichiometric amounts of alkyllithium and alcohol.

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peri-Nitrosamine Interactions. 2. *trans*-1,8-Dinitroso-1,8-diazadecalins

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An X-ray crystal structure of *trans*-1,8-dinitroso-1,8-diazadecalin (**5**) shows that in the crystal the nitroso groups adopt a syn,anti orientation and that the diazadecalin ring adopts a chair,twist-boat conformation. The chair,twist-boat conformation is apparently adopted so as to allow sufficient separation between the nitroso groups to avoid van der Waals interactions between them. Proton, ^{13}C, and ^{15}N NMR spectra of **5** and its 10-methyl analogue **6** show that they exist in solution mainly as the syn,anti rotamers with progressively lesser amounts of the anti,anti and syn,syn rotamers present. The results necessitate a reinterpretation of the previously reported "weak bonding interaction" between the nitroso groups of *trans*-1,4,5,8-tetranitroso-1,4,5,8-tetraazadecalin (**1**), which also shows a preference for syn,anti rotamers and which was assumed to exist in a chair,chair conformation.

Introduction

We recently reported on the unusual rotamer distribution and ^{15}N NMR chemical shifts of the nitroso nitrogens in *trans*-1,4,5,8-tetranitroso-1,4,5,8-tetraazadecalin[1] (**1**). We concluded that **1** exists in solution as an 88:12 mixture of rotamers **1c** and **1d** (see Figure 1) with perhaps a small amount of rotamers **1a** and **1b** present. We reasoned that both the rotamer distribution and ^{15}N chemical shifts could be explained by the existence of a "weak bonding interaction" between the oxygen atom of a syn nitroso group and the nitroso nitrogen of an anti nitroso group in a 1,8- (or 4,5-) syn,anti conformation (see Figure 2) and an electrostatic repulsion between like charges which destabilizes rotamer **1b**. We assumed that the three additional possible rotamers with 1,8- (or 4,5-) syn,syn conformations (i.e., **1e**–**1g**) were highly improbable since it was likely that the tetraazadecalin moiety of **1** was in a double chair conformation[2] and two oxygen atoms could not occupy the same space in the 1,8-syn,syn conformations. We will show, from new work reported in this paper and from recent work in other laboratories[3] on the related tetraacyltetraazadecalins, that the assumption that the tetraazadecalin moiety of **1** must adopt a double chair conformation is erroneous.

Further work on **1** to gain a better understanding of its unusual rotamer distribution and ^{15}N chemical shifts was hampered by its extremely low solubility and our inability

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