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# SUBSTITUTION AND ADDITION REACTIONS OF ORGANIC SUBSTRATES WITH HYPOFLUOROUS ACID

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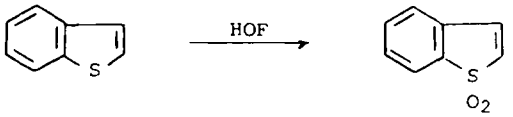
**Abstract**—The chemical reactions of hypofluorous acid with aromatic and olefinic substrates show considerable variety. Hypofluorous acid reacts with naphthalene to give 1-naphthol, 2-naphthol and 1,4-naphthoquinone; with benzo[b]thiophen to give the 1,1-dioxide; with *trans*-stilbene to give *threo*-2-fluoro-1-hydroxy-1,2-diphenylethane, benzophenone and diphenylacetaldehyde; and with cholesteryl acetate to give the two epoxides ($\alpha:\beta$ = 6.3:1) and two fluorohydrins (6$\beta$-fluoro-5$\beta$-ol and 5$\alpha$-fluoro-6$\beta$-ol).

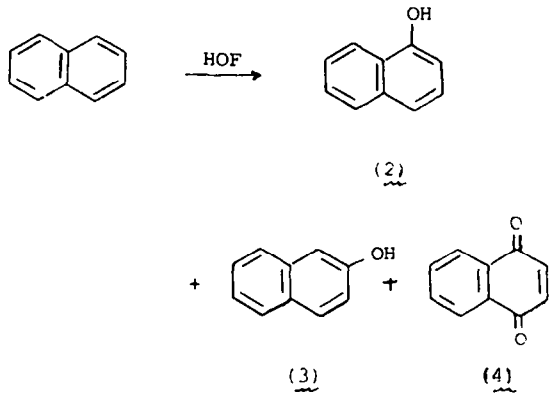
In earlier papers we have shown that hypofluorous acid hydroxylates simple aromatic systems[1] and adds to alkenes to give fluorohydrins.[2] We have now extended this study by identifying the by-products and an intermediate formed in the reaction with naphthalene, and by examining the reactions with *trans*-stilbene and cholesteryl acetate in order to determine the stereochemistry of the addition. We observe at the outset that hypofluorous acid occasionally detonates,[3] and we consider it hazardous to prepare this reagent in quantities greater than 100 mg.

In our original experiments with naphthalene we found the 1- and 2- naphthols, as expected, together with two by-products.[1] The less polar of these has been identified, by GC-MS and by comparison with authentic material, as 1,4-naphthoquinone, which evidently arises by the further substitution and oxidation of 1-naphthol. GC-MS studies suggested that the second by-product was derived from benzo[b]thiophen present as a reactive impurity in commercial naphthalene. This has been confirmed by comparison with an authentic sample of benzo[b]thiophen-1,1-dioxide (**1**);[3] and by examining the reaction of benzo[b]thiophen with hypofluorous acid, which gave the 1,1-dioxide in 74% yield.




(1)

The reaction of hypofluorous acid with a zone-refined sample of naphthalene in carbon tetrachloride gave none of this material, but gave 1-naphthol (**2**, 2.9%), 2-naphthol (**3**, 0.75%) and 1,4-naphthoquinone (**4**, 7.4%). Yields were somewhat variable, possibly because of the difficulty in reproducing exactly the quantity and delivery of the stream of hypofluorous acid in the inert carrier gas. In the present experiments we have found yields of 1-naphthol up to 5%, and 2/3 ratios in the range 3–4.5. We have not been able to reproduce the higher yields recorded earlier for this reaction.[1]




(2) (3) (4)

We have speculated[1] that the reaction of aromatic compounds with hypofluorous acid might proceed through the arene oxides. Treatment of naphthalene in carbon tetrachloride containing anhydrous sodium carbonate to dispose of any hydrogen fluoride, followed by TLC[4] without further workup, provided presumptive evidence for the formation of naphthalene-1,2-oxide. A component appeared with the same $R_f$ as an authentic sample of the oxide, and on two-dimensional chromatography it decomposed to naphthol in accordance with the conclusion that the 1,2-oxide had been formed. However, the decomposition of the 1,2-oxide is known to give principally 1-naphthol.[4] In our experiments, the decomposition of naphthalene-1,2-oxide in air at room temperature, or in carbon tetrachloride containing a trace of ethereal hydrogen chloride, followed by analysis by GLC, revealed a 2/3 ratio of about 19. In the reaction of hypofluorous acid with naphthalene the position is not clearcut, because the naphthols are more reactive

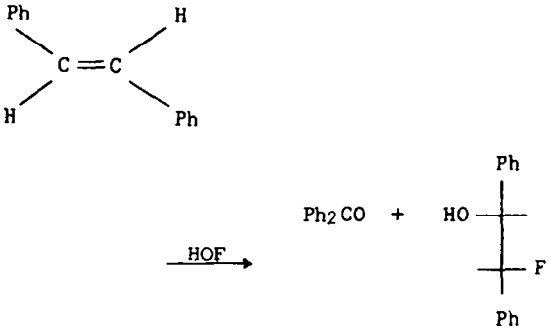
than is naphthalene; however, the apparent 2/3 ratio is only about 7 even when allowance is made for 1,4-naphthoquinone, and it therefore appears that a second route must also exist, at least for the formation of 2-naphthol

Earlier work on the reaction of hypofluorous acid with alkenes has shown that fluorohydrins are formed.[2] The examples then chosen did not permit ready examination of the stereochemistry of the reaction, and two further reactions have now been studied with this in mind.

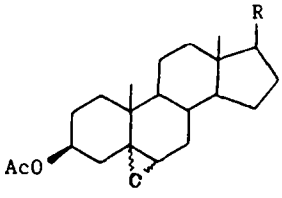
*trans*-Stilbene in dichloromethane was reacted with hypofluorous acid in the usual way. After treating the reaction mixture with anhydrous sodium carbonate the identified products were benzophenone (8%) and *threo*-2-fluoro-1-hydroxy-1,2-diphenylethane (**5**; crude yield 26%; recrystallised 16%). The epoxide was not detected nor was the *erythro*-fluoroalcohol. The compound was detected as an unstable component of the product mixture by TLC: it is known to autoxidise readily on chromatographic supports to give benzophenone.[5] The fluorohydrin (**5**) did not appear to be changed on chromatography.

*cis*-Addition of this sort is not commonly encountered, but has prior example with reagents which are highly reactive. Thus selective *cis*-addition to *trans*-stilbene has been observed with trifluoromethyl hypofluorite[6] and with trifluoroacetyl hypofluorite.[7]

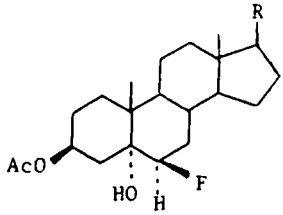
With the hindered alkylated olefin, cholesteryl acetate, the reaction was quite different, and here both epoxides and fluorohydrins were obtained. The α-epoxide (**6**) was isolated in 51% yield. The corresponding β-epoxide (**7**) was detected, but was not isolated. Attack at the less hindered α-face is evidently preferred even with this reactive agent (α/β ratio = 6.3). Two fluorohydrins were isolated in




(5)




(6, α-epoxide)
(7, β-epoxide)

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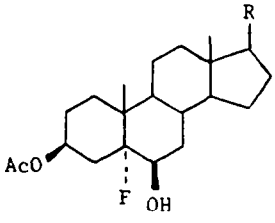
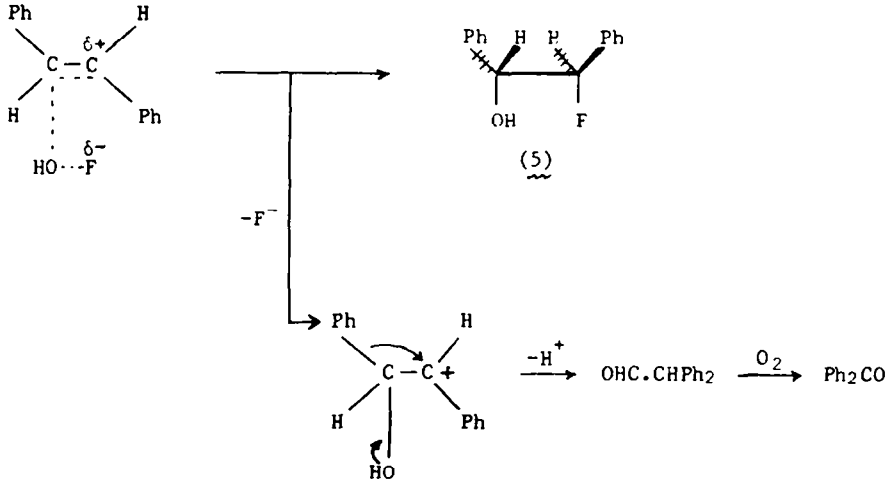



(9)

reaction is rationalised in the scheme, which suggests that if a direct *cis*-addition of hypofluorous acid does not occur (presumably via a tight ion pair) to give (**5**), then a 1,2-phenyl shift supervenes over *trans*-addition to give diphenylacetaldehyde. The latter




Scheme 1.

yields of about 7% each: the 6β-fluoro-5α-ol (**8**) and the 5α-fluoro-6β-ol (**9**). No products of *cis*-addition of hypofluorous acid and no rearrangement products were identified. Such products, if formed, can only have been minor components of the product mixture.

In earlier papers[1,2] we have postulated the intermediacy of oxide species in reactions of hypofluorous acid with double bond systems. This proposal has now received experimental support by the detection of naphthalene 1,2-oxide and by the isolation of the epoxides (**6**,**7**). However, the results with the olefins studied are notably different. We have not detected the epoxide with *trans*-stilbene, and *cis*-addition of HOF predominates. On the other hand epoxide formation predominates with cholesteryl acetate, and the fluorohydrins which are formed are the products of *trans*-addition. Separate experiments have shown that the fluorohydrins are not effectively converted to the epoxides under the mild workup conditions.

Hypofluorous acid as normally prepared inevitably contains some hydrogen fluoride. Additional hydrogen fluoride must be generated in some reactions (e.g. aromatic hydroxylation). Hydrogen fluoride might be expected to take part in the reaction in two ways.

(i) *By interaction with hypofluorous acid.* This could occur by protonation at oxygen, which might generate an electrophilic fluorine species ($H_2\overset{+}{O}$–F). An alternative, which we regard as more likely, is molecular association with incipient fluoride, to give an electrophilic hydroxy species ($HO\overset{\delta+}{---}\overset{\delta-}{F}---H$–F). The majority of reactions of hypofluorous acid which have so far been examined, and which are relevant to the question, accord with the latter polarisation.

(ii) *By opening an epoxide to give a fluorohydrin.* Indeed, the *cis*-cleavage of a *trans*-stilbene oxide by hydrogen fluoride would offer an alternative rationalisation for the formation of **5**, and such *cis*-opening of epoxides is known with aryl-substituted epoxides (e.g. Ref. 8, benzoate opening of *trans-p*-methoxystilbene oxide). However, in reactions of HOF with simple trisubstituted olefins the epoxides have not been detected, although the fluorohydrin products have been rationalised in terms of protonated epoxide intermediates.[2]

## EXPERIMENTAL

TLC was carried out on silica (Merck or Kodak), the developing solvent being 40–60° petroleum ether:acetone = 9:1 unless otherwise stated.

The following GLC equipment was used. System A: Hewlett Packard 5830A with flame ionisation detector at 250°, 10% Carbowax 20M on Diatomite C-AW 80/100 mesh, o.d. 1/8 in. × 5 ft, 200°, nitrogen carrier at 20 ml $min^{-1}$. System B: Perkin–Elmer 900 with flame ionisation detector at 250°, "Ultra-Bond" PEGS 100/120 mesh, o.d. 1/8 in. × 6 ft, 200°, injection 230°, helium carrier at 40 ml $min^{-1}$. GCMS: Perkin–Elmer 270. High resolution mass spectra: AEI Ltd. MS902. $^1H$ NMR: Bruker WP80 with TMS as internal reference. $^{19}F$ NMR: Nicolet 200 with $CFCl_3$ as internal reference.

Hypofluorous acid was prepared and manipulated as previously described.[1,2] The $CCl_4$ used as solvent was of AR S-free quality.

### *Reaction of naphthalene with hypofluorous acid*

*Detection of naphthalene-1,2-oxide.* An ice-cold mixture of naphthalene (2 g) $CCl_4$ (8 ml) and solid $Na_2CO_3$ (0.6 g) was treated with a stream of HOF (~25 mg) in $N_2$ over a period of 5 min. The yellowish mixture was filtered, and the filtrate was submitted to TLC without further processing. This revealed an unstable component which had the same $R_f$ (0.43) as that of naphthalene-1,2-oxide, together with 1- and 2-naphthol. Two-dimensional TLC showed that this compound decomposed to give 1-naphthol.

*Naphthols from the decomposition of naphthalene-1,2-oxide.* A sample of naphthalene-1,2,-oxide[9] (10 mg) was kept in the solid state at room temp (18–20°) for 50 hr. It was dissolved in ether and examined by GLC (system A), which showed that it had decomposed to give 1-naphthol (relative abundance 95%, $R_v$ = 880 ml), together with a small amount of 2-naphthol (relative abundance 5%, $R_v$ = 1010 ml). TLC showed small amounts of other decomposition products, but these were not detected by GLC.

A second sample of naphthalene-1,2-oxide was allowed to decompose in $CCl_4$ containing a trace of acid (ethereal HCl). GLC analysis showed a similar ratio of naphthols to that observed before.

*Recognition of products from naphthalene containing benzo[b]thiophen impurity.* Naphthalene (1 g, described as an "organic standard") in $CCl_4$ (5 ml) was treated with HOF (*ca* 25 mg) in a stream of $N_2$ at room temp. The delivery was complete within 5 min. After a further 10 min the mixture was washed with water (8 ml), the aqueous extract being back extracted with ether (8 ml). A small amount of dark solid in the tip of the delivery tube was dissolved in ether. The combined organic solns were dried ($Na_2SO_4$), filtered, and evaporated nearly to dryness. The residue was dissolved in $CHCl_3$ for GLC (system B), which revealed 1,4-naphthoquinone (90 ml, 6.5%, calc. on 3HOF), 1-naphthol (380 ml, 3.1%), 2-naphthol (450 ml, 1.1%) and benzo[b]thiophen-1-dioxide (590 ml, 1.3%, calc. on 2HOF for purposes of comparison).

The naphthols had already been identified as products of this reaction.[1] This identification was confirmed, and the 1,4-naphthoquinone and benzo[b]thiophen-1-dioxide were identified by mixed GLC with authentic compounds, and by GCMs and high resolution mass spectra. 1,4-Naphthoquinone: *m/e* 158 (M, 100%), 130 (43%). (Found: $M^+$ 158.035. $C_{10}H_6O_2$ requires 158.037.) 1-Naphthol: *m/e* 144 (M, 100%), 115 (90%). (Found: $M^+$ 144.058. $C_{10}H_8O$ requires 144.058.) 2-Naphthol: *m/e* 144 (M, 100%), 115 (75%). Benzo[b]thiophen-1,1-dioxide: *m/e* 166 (M, 30%), 137 (100%). (Found: $M^+$ = 166.007. $C_8H_6O_2S$ requires 166.009.)

*Treatment of zone-refined naphthalene with hypofluorous acid.* Naphthalene (1.03 g, zone refined) was dissolved in $CCl_4$ (5 ml) and treated with HOF (*ca* 25 mg) in a stream of $N_2$ at room temp (delivery time *ca* 5 min). The naphthalene soln became highly coloured, and a dark deposit formed inside the delivery jet. The reaction soln was transferred with $CHCl_3$ (3 ml) and washed with water (8 ml), which was back extracted with ether (8 ml). The soln was dried ($Na_2SO_4$) and subjected to GLC (system B). The black material in the jet was dissolved in acetone–$CHCl_3$ and subjected to GLC in the same system. In this way the material in the jet was found to contain 1,4-naphthoquinone (2.9%, calc. on 3HOF), while in the soln 1-naphthol (2.9%), 2-naphthol (0.75%), and 1,4-naphthoquinone (4.5%, calc. on 3HOF) were detected.

In other experiments with zone-refined naphthalene, yields of 1-naphthol of up to 5%, and 1-naphthol/1-naphthol ratios of up to about 4.5 have been observed.

*Reaction of benzo[b]thiophen with hypofluorous acid.* Benzo[b]thiophen (2.01 g, ≥99%) in $CCl_4$ (8 ml) was treated over 90 min with a stream of HOF generated by passing $N_2$ over HOF (100 mg) at −50°. During the treatment the volume of the solvent was restored to the original from time to time. A pale solid deposited in the inside of the delivery tube and was examined separately.

The main soln was kept for 2 hr and then washed with water (5 ml), the aqueous extract being back extracted with ether (2 ml). The organic solns were combined, dried ($Na_2SO_4$) and filtered. The deposit in the delivery tube was dissolved in $CHCl_3$. Both solns were subjected to GLC

(system B). The main soln was found to contain benzo[b]thiophen-1,1-dioxide (9%, calc. on 2HOF) together with several unidentified trace components. The material on the delivery tube was found to contain a further quantity of benzo[b]thiophen-1,1-dioxide (65%, calc. on 2HOF) which on isolation and crystallisation from water gave 79 mg (34%) of the sulphone as an off-white solid, m.p. and mixed m.p. 140–143° (lit.[3] m.p. 142–143°).

*Reaction of trans-stilbene with hypofluorous acid.* A soln of *trans*-stilbene (0.72 g) in $CH_2Cl_2$ (8 ml) at 0° was treated over 45 min with a stream of HOF generated by passing $N_2$ over hypofluorous acid (*ca* 100 mg) at −50°. A slight darkening of the soln was observed during this time. Anhyd $Na_2CO_3$ (1.05 g) was added, and the mixture was kept overnight, filtered, and evaporated to dryness.

The residue was applied in $CHCl_3$ to preparative plates and eluted with $CH_2Cl_2$ to give the following components in order of decreasing mobility. $R_f$ 0.8, starting material (0.11 g). $R_f$ 0.6, $R_f$ 0.5, $R_f$ 0.3, three related components: on chromatography and rechromatography, the material $R_f$ 0.5 was formed from the other components, and was identified as benzophenone, colourless oil (0.106 g) giving colourless needles, m.p. 46–47° (lit.[10] m.p. 47–48°) from ether (43 mg, 8%). $R_f$ 0.1, an amorphous product (0.157 g, crude yield = 26%) which gave colourless rods (0.095 g, 16%) with m.p. 92.5° from $CHCl_3$ identified (TLC, IR) with an authentic sample (crystallised from hexane as needles, m.p. 99–100°, lit. m.p. 102–103°,[6] 99°[7]) of *threo*-2-fluoro-1-hydroxy-1,2-diphenylethane. (Found: $M^+$ 216.095. $C_{14}H_{13}OF$ requires M = 216.095.) δ ($CDCl_3$) $PhC_AHOH.C_BHFPh$ 2.80 (OH, t, J = 2.5 Hz, ex), 4.92 ($H_A$, d,d,d, $J_{AB}$ = 7 Hz, $H_{AF}$ = 13 Hz, $J_{AOH}$ = 2.5 Hz), 5.42 ($H_B$, d,d, $J_{AB}$ = 7 Hz, $J_{BF}$ = 47 Hz), 7.2 (m, ArH). TLC comparison with authentic samples of *trans*-stilbene oxide and *erythro*-2-fluoro-1-hydroxy-1,2-diphenylethane did not reveal these components.

The literature preparation[6,11] of *threo*-2-fluoro-1-hydroxy-1,2-diphenylethane by the reaction of *trans*-stilbene oxide with $BF_3$ gave a by-product, $R_f$ 0.58, identified chromatographically with the unstable component, $R_f$ 0.60, above. The literature preparation was repeated to isolate this component, which was thereby identified as diphenylacetaldehyde. $M^+$ 196, ν 1715 $cm^{-1}$, δ($CDCl_3$) 4.83 (d, $J_{AB}$ = 2.5 Hz, $Ph_2\underline{C}H$), 7.25 (m, ArH), 9.78 (d, $J_{AB}$ = 2.5 Hz, −CHO). (The third component, $R_f$ 0.3, of the inter-related trio observed in the HOF–stilbene reaction is presumably 2-hydroperoxy-2,2-diphenylacetaldehyde.[5])

*Cholesteryl acetate.* A soln of cholesteryl acetate (1.71 g) in $CH_2Cl_2$ (20 ml) at 0° was treated with a stream of HOF generated by passing $N_2$ over HOF (100 mg) at −50° during 1 hr. After a further 10 min the soln was washed with $NaHCO_3$ and water, dried ($Na_2SO_4$), filtered, and evaporated to dryness. The mixture was subjected to preparative TLC (petroleum : diethyl ether = 4 : 1, three elutions) to give the following components in order of decreasing mobility. Cholesteryl acetate, $R_f$ 0.81, 0.31 g. 3β-Acetoxy-5β,6β-epoxycholestane and 3β-acetoxy-5α,6α-epoxycholestane were both present in the band $R_f$ 0.56 in the ratio β : α = 71 : 29 [based on the integration of the NMR doublets at δ2.87 (β) and δ3.06 (α) respectively]. Total yield = 0.176 g (14%). β-Acetoxy-5α,6α-epoxycholestane, $R_f$ 0.50, crystallised from ethanol, 0.63 g (51%) with m.p. 95–96°, lit. m.p. 98°,[12] 101–103°.[13] 3β-Acetoxy-6β-fluorocholestan-5α-ol, $R_f$ 0.24, m.p. 211°, mixed m.p. 211–212° (lit.[14] m.p. 207–9°); 96 mg (7%) after crystallisation from MeOH. (Found: $M^+$ 464.368. $C_{29}H_{49}O_3F$ requires 464.367.) $\nu_{max}$ (KBr) 3410, 1737, 1700 $cm^{-1}$. δ($CDCl_3$) 5.12 (bm, 3–H), 4.21 (bd, $J_{HF}$ = 49 Hz, 5–H), 2.02 (s, Ac), 1.72 (s, OH, ex), 1.12 (d, $J_{HF}$ = 4 Hz, Me 19) and 0.68 (s, Me 18). $^{19}F$ NMR($CDCl_3$) δ −181.0 (m).

3β-Acetoxy-5α-fluorocholestan-6β-ol, $R_f$ 0.19, m.p. 166–167° (lit. m.p. 171–172°,[14] 168–169°[15]), colourless crystals (98 mg, 7%) from MeOH. (Found: $M^+$ 464.367.) $\nu_{max}$ (KBr) 3510, 1725, and 1687 $cm^{-1}$. δ($CDCl_3$) 5.04 (m, 3–H), 3.70 (m, 6–H), 2.01 (s, Ac), 1.56 (s, OH, ex), 1.15 (d, $J_{HF}$ = 0.5 Hz, Me–19), and 0.68 (s, Me–18). $^{19}F$ NMR ($CDCl_3$) δ −161.2 (d, $J_{6\beta H,F}$ = 4 Hz).

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