REACTIONS OF 8H-FURO[3,4,-d]DIBENZ[b,f]AZEPINE AND 9H-TRIBENZ[b,d,f]-AZEPINE WITH t-BUTYL HYPOCHLORITE AND SILVER TRIFLUOROACETATE. ATTEMPTS TO FORM A LONG-LIVED AROMATIC NITRENIUM ION

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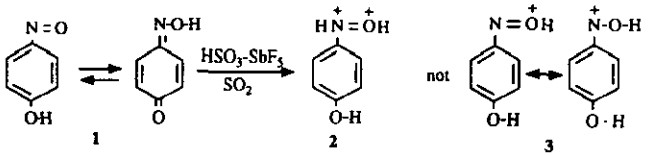
Abstract - Attempts to prepare aromatic and thus potentially long-lived nitrenium ions from 8H-furo[3,4-d]dibenz[b,f]azepine (**19**) and 9H-tribenz[b,d,f]azepine (**34**) were unsuccessful. Reaction of **19** with t-butyl hypochlorite results in chlorination of the furan ring (**25**), while reaction of **19** with silver trifluoroacetate forms a mixture of the cis- and trans- dimethoxydihydrofurans (**32**) and (**33**). Reaction of **34** with t-butyl hypochlorite leads to a mixture of mono-, di- and trichloroazepines (**37-42**). The reaction of silver trifluoroacetate with **34** yields silver metal and unreacted **34**.

Although nitrenium ions are not as well known or as thoroughly studied as their carbon analog, the carbocation, they are well established as intermediates in many reactions.[1] Nitrenium ions have captured the interest of a variety of investigators for a number of reasons including their synthetic utility[2] and their implication as the penultimate carcinogen derived from certain carcinogenic nitrogen containing compounds.[3] While their place as unstable intermediates in certain reactions has widespread acceptance, relatively little work has been undertaken to generate stable and thus potentially long-lived nitrenium ions. Olah[4] investigated the protonation of several benzoquinone monooximes (**1**) in "magic acid" (Scheme I). Evidence suggests that the monoprotonated product [the nitrenium ion (**3**)] is not formed but instead the diprotonated product (**2**) is the predominant species under these conditions.

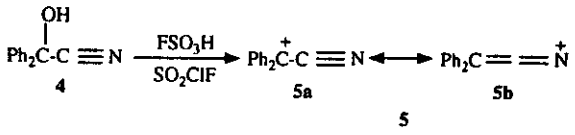
Scheme I



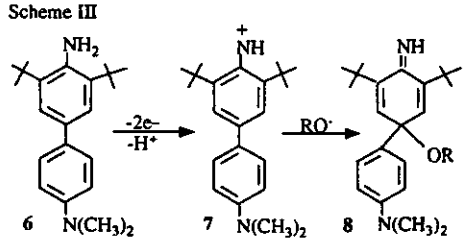
In another study Olah[5] investigated the reaction of benzophenone cyanohydrin (**4**) with FSO_3H/SO_2ClF (Scheme II). Analysis of the reaction mixture by nmr indicates the cation (**5**) is present and **5b**, the nitrenium ion form, contributes significantly to the overall structure of the cation.

A second report of a successful generation of a long-lived nitrenium ion was made by Rieker and Speiser.[6] Electrochemical oxidation of the aniline (**6**) results in the long lived (in solution) biphenylnitrenium ion (**7**). Addition of alkoxides to a solution of **7** results in nucleophilic attack to yield an aminoquinol ether (**8**) (Scheme III).

Scheme II

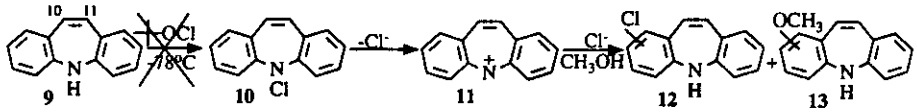


Scheme III



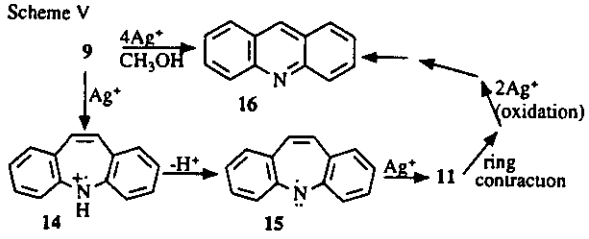
We have made previous attempts to prepare the aromatic (and thus potentially long-lived) nitrenium ion, dibenz[b,f]aztropylium ion (**11**). Gassman[7] has shown that arylamines react with t-butyl hypochlorite to form N-chloroamines which subsequently decompose by loss of chloride ion to yield arylnitrenium ions. By analogy to Gassman's work we envisioned production of **11** via Scheme IV. In contrast to the rather simple expected product mixture of **12** and **13**, arising from nucleophilic attack on **11**, a very complicated product mixture was found consisting primarily of acridines from ring contraction of **9**.[8] It is likely that **10** is not produced in this reaction but the positive chlorine attacks the electron rich double bond at the 10, 11 position of **9** thus leading to the complicated product mixture.

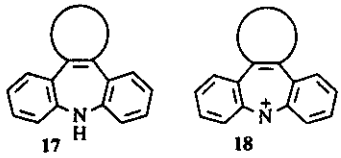
Scheme IV



In a second attempt to produce **11** we reacted **9** with silver (I).[9] By analogy to the electrochemical oxidation in Scheme III, removal of two electrons and deprotonation via chemical oxidation of **9** by silver(I) should produce **11** (Scheme V). This reaction yields acridine in 94% yield. It is conceivable that **11** is formed as an intermediate in this process however, it is unstable under the reaction conditions undergoing ring contraction and further oxidation.

Scheme V

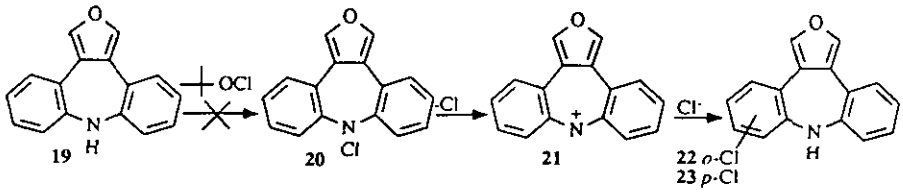




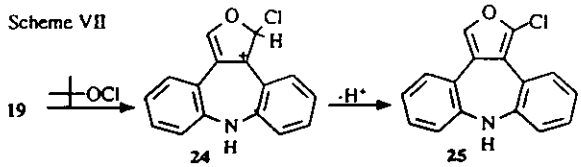
It was clear that if we expected to generate long-lived azatropylium ions such as **11** that the double bond at the 10, 11 position of **9** had to be inactivated. We believed this could be accomplished by preparing [b,d,f]tetracyclic azepines (**17**) followed by conversion to the nitrenium ion (**18**). Previously we have described our syntheses of 8H-furo[3,4-d]dibenz[b,f] azepine (**19**)[10] and 9H-tribenz[b,d,f]azepine (**34**).[11] We report here our attempts to prepare the aromatic and thus potentially long-lived nitrenium ions furo[3,4-d]dibenzazatropylium ion (**21**) and tribenz[b,d,f]azatropylium ion (**36**) from **19** and **34** respectively.

Compound (19) was reacted with one equivalent of t-butyl hypochlorite at -78°C with the intent of producing the N-chloroazepine (20), and with subsequent loss of chloride the desired nitrenium ion (21) (Scheme VI). The formation of 21 would be evident by the formation of the ortho- and para-chloro benzo substituted products (22) and (23) resulting from nucleophilic attack of the chloride ion on the delocalized ion (21). Analysis of the reaction mixture by GCms shows only one product, and the mass spectrum of this product is consistent with monochlorination of 19. The parent ion and base peak of this product is m/z = 267 and the next highest peak is m/z = 204. We believe the peak at 204 results from loss of ClCO indicating the chlorine is attached to the furan ring and not to the benzene ring as in 22 and 23. This fragmentation along with the fact that only one monochlorination product is observed (not two as in 22 and 23) is consistent with chlorination of the furan ring to yield 25 and not the benzo substituted products (22) and (23). The chlorinated furan (25) likely forms via direct electrophillic aromatic substitution on the furan ring through 24 (Scheme VII) and not via the desired nitrenium ion (21) and thus no attempts were made to isolate or further identify this product.

Scheme VI

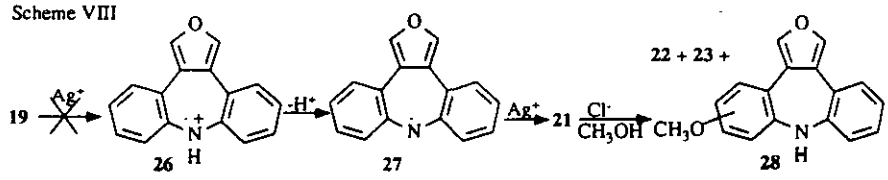


Scheme VII



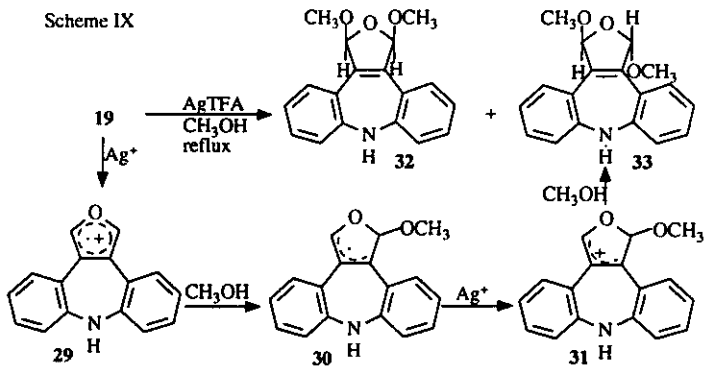
A second attempt at the production of the nitrenium ion (21) was via chemical oxidation of 19. As noted earlier, electrochemical oxidation of aromatic amines[6] produces aryl nitrenium ions (Scheme III) and chemical oxidation with silver (I) of the azepine (9) may proceed by the nitrenium ion (11) (Scheme V).[9] An analogous oxidation of 19 with silver trifluoroacetate in methanol should result in the nitrenium ion (21) (Scheme VIII). Nucleophilic attack on 21 would result

Scheme VIII



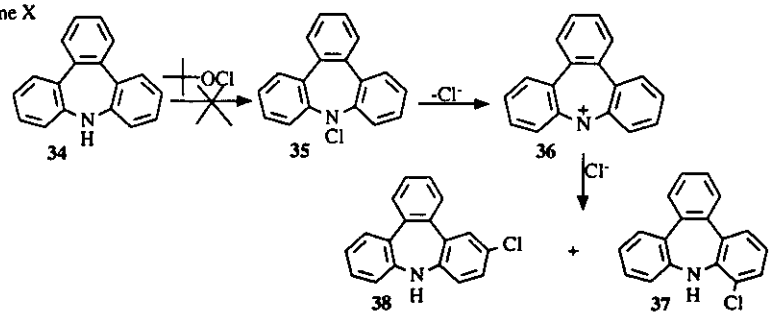
in the chloro and methoxy substituted products (22), (23), and (28). However column chromatography of the reaction mixture yields two products whose structures are tentatively identified by nmr and ms as the cis- (79%) and trans- (20%) dimethoxydihydrofurans (32) and (33). The ^{1}Hnmr shows the trans- methoxy groups of 33 at δ3.45 and the cis-methoxy groups of 32 (because of their closer proximity) downfield at δ3.54. Assignment of the stereochemistry of 32 and 33 by nmr has

Scheme IX



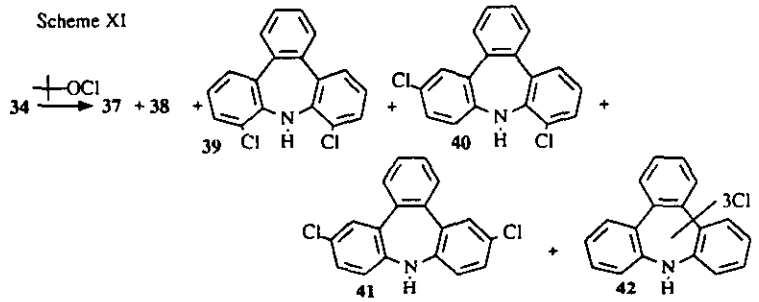
precedent in the literature.[12] A similar formation of cis- and trans-dimethoxydihydrofurans has been observed with the anodic oxidation of furans[13] in methanol and these reactions are believed to occur by initial formation of a radical cation. By analogy 32 and 33 can be reasonably accounted for by the radical cation mechanism shown in Scheme IX. As expected from Scheme IX, addition of one equivalent of silver(I) results in 32, 33, and the starting furan (19) while addition of two equivalents of silver(I) as shown by a GCms of the reaction mixture yields only 32 and 33. It is also interesting to note that unlike 19 the N-acetyl derivative of 19 does not react with silver trifluoroacetate in refluxing methanol. Apparently the strong electron releasing effect of the free amine in 19 is necessary for the formation of the radical cation (29) while the amide nitrogen in the N-acetyl derivative of 19 does not provide enough stabilization to form an analogous radical cation. Since the formation of 32 and 33 was not likely through the desired nitrenium ion (21) no further effort was made to purify or identify these solids. Although the azepine (19) does not suffer from the ring contraction problem that plagues 9, the furan ring in 19 provides a site for facile reactions with t-butyl hypochlorite and silver (I). We thus turned our attention to the reaction of 9H-tribenz[b,d,f]azepine (34) with these same reagents in pursuit of the nitrenium ion tribenz[b,d,f]azatropylium ion (36). Analysis of the reaction of 34 with one equivalent of t-butyl hypochlorite by GCms indicates that chlorination has occurred to yield two monochlorinated isomers, three dichlorinated isomers, one trichlorinated isomer (minor product) and unreacted 34. If the monochlorinated products are the ortho- and para- isomers (37) and (38), formation of these products could be via the desired N-chlorinated tribenzazepine (35), followed by loss of chloride to yield the delocalized nitrenium ion (36), with subsequent attack at the ortho and para positions by the nucleophilic chloride ion (Scheme X). Furthermore, the dichlorinated (with

Scheme X



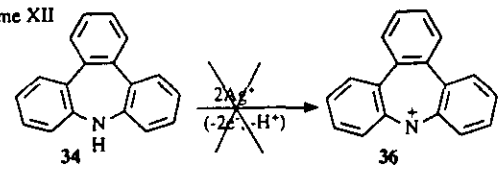
possible structures **39**, **40**, and **41**) and trichlorinated products (**42**) could be accounted for by analogous attack on the monochlorinated and dichlorinated adducts respectively. However, direct electrophilic aromatic chlorination of **34** also readily accounts for these mono-, di- and trichlorinated products. In an effort to distinguish between these two mechanisms, methanol was added to the reaction mixture. In the presence of methanol the same chlorinated products are formed (tentatively identified as **37-42**) while no methoxy substituted products were observed. This suggests the absence of the nitrenium ion (**36**), since this intermediate should be susceptible to attack by the nucleophilic methanol. Thus direct electrophilic aromatic chlorination is likely occurring. Although the mass spectra of the chlorinated products does not allow for the assignment of specific positions for the chlorine atoms, some tentative conclusions might be drawn. Electrophilic aromatic substitution of **34** should yield the ortho- and para- monochlorinated products (**37**) and (**38**) since the nitrogen in **34** strongly activates the adjacent rings and is a strong ortho-, para- director. Furthermore it is reasonable to assign the dichlorinated products as (**39**), (**40**), and (**41**) in light of the ortho-, para- directing power of the nitrogen, coupled with the deactivation by the first chlorine, would yield ortho-, para- products but with the second chlorine attacking the unsubstituted ring. No attempts to isolate and further identify these structures was made.

Scheme XI



In an attempt to produce the nitrenium ion (**36**) by oxidation/deprotonation/oxidation (Scheme XII), **34** was dissolved in methylene chloride and reacted with two equivalents of silver trifluoroacetate in methanol under reflux. The reaction mixture turns green (an indication that the radical cation of **34** may be forming) and becomes cloudy. After twenty hours, filtration of the reaction mixture yields silver metal (83%) and after workup of the remainder of the reaction mixture the starting tribenz[b,d,f]azepine (**34**) is isolated in quantitative yield. Under the same reaction conditions in the absence of **34** no silver metal is formed. Formation of silver metal in the presence of **34** may be a result of the catalytic oxidation of methanol by the radical cation of **34**. This reaction is presently under further investigation.

Scheme XII



EXPERIMENTAL

All chemicals were purchased from Aldrich Chemical Co., Milwaukee, WI, and were used without further purification. GCms were obtained on a Hewlett Packard Model 5995C equipped with a Hewlett Packard HP-1 crossed linked methyl silicone gum capillary (25 m x 0.2 mm x 0.33 μm film thickness) oven temperature 150° to 250°C @ 10°/min and hold for 25 min; nuclear magnetic resonance spectra were recorded on a Varian Gemini 300 (^{1}H, 300 MHz; ^{13}C, 75 MHz). 8H-Furo[3,4-d]dibenz[b,f]azepine (**19**),[10] 9H-tribenz[b,d,f]azepine (**35**)[11] and t-butyl hypochlorite[14] were prepared according to the literature.

Reaction of 8H-Furo[3,4,-d]dibenz[b,f]azepine (19) with t-Butyl Hypochlorite.

8H-Furo[3,4-d]dibenz[b,f]azepine (**19**) (50 mg, 0.22 mmol) was dissolved in 5 ml of methylene chloride and cooled to -78°C in a flask equipped with a calcium chloride drying tube. To this solution was added dropwise t-butyl hypochlorite (24 mg, 0.22 mmol) in 5 ml of methylene chloride while maintaining the temperature at -78°C. The solution is stirred at -78°C for greater than 1 h and allowed to warm to room temperature and stirred overnight. An aliquot was removed and analyzed by GCms. GCms reveals two products: the starting material (**19**) (retention time 13.71 min) and a monochlorinated product (tentative structure **25**) (retention time 15.85 min): m/z 269(31%), 268 (20), 267 (M^+, 100), 204 (41), 203 (16), 202 (9), 176 (8).

Reaction of 8H-Furo[3,4-d]dibenz[b,f]azepine (19) with Silver Trifluoroacetate. Formation of cis- and trans-1,3-Dimethoxy-,3-dihydro-8H-furo[3,4-d]dibenz[b,f]azepine (32 and 33).

8H-Furo[3,4-d]dibenz[b,f]azepine (**19**) (200 mg, 0.86 mmol) and silver trifluroacetate (397 mg, 1.72 mmol) were dissolved in 30 ml of methanol and the solution was refluxed for 20 h. The reaction mixture was filtered to yield 182 mg (98%) of silver metal. The methanol was evaporated under vacuum from the filtrate and the residue was chromatographed on 5 g of silica gel. Elution with carbon tetrachloride/methylene chloride (ratio 9:1) gave as a crude solid (tentative structure **33**) (51 mg, 20% from **19**): δ_H ($CDCl_3$) 3.45 (s, 6H, OMe), 5.00 (br s, 1H, NH) 6.23 (s, 2H), 6.62 (d, J=7.6 Hz, 2H), 6.93 (t, J=7.5 Hz, 2H), 7.15 (t, J=7.6 Hz, 2H), 7.28 (d, J=7.5 Hz, 2H); δ_C ($CDCl_3$) 52.4, 108.1, 119.9, 123.4, 125.3, 127.9, 130.6, 138.1, 149.1; GC retention time 17.58 min; m/z 296 (M+1, 20%), 295 (M+, 100), 264 (75), 263 (61), 249 (41), 248 (55), 236 (35), 221 (35), 220 (96), 204 (46), 192 (20), 191 (36), 190 (29), 165 (59). Elution with methylene chloride gave as a crude solid (tentative structure **32**) (200 mg, 79% from **19**): δ_H ($CDCl_3$) 3.54 (s, 6H, OMe), 5.00 (br s, 1H, NH) 5.99 (s, 2H), 6.62 (d, J=7.6 Hz, 2H), 6.92 (t, J=7.5, 2H), 7.14 (t, J=7.6 Hz, 2H), 7.21 (d, J=7.5 Hz, 2H); δ_C ($CDCl_3$) 53.6, 107.1, 120.1, 123.3, 125.3, 127.9, 130.7, 137.6, 149.6; GC retention time 18.28 min; m/z 296 (M+1, 18%), 295 (M+, 89), 264 (67), 263 (100), 249 (38), 248 (78), 236 (32), 221 (28), 220 (89), 204 (24), 192 (14), 191 (24), 190 (22), 165 (47).

Reaction of 9H-Tribenz[b,d,f]azepine (34) with t-Butyl Hypochlorite.

9H-Tribenz[b,d,f]azepine (**34**) (25 mg, 0.10 mmol) was dissolved in 2 ml of methylene chloride and cooled to -78°C in a flask

equipped with a calcium chloride drying tube. To this solution was added dropwise t-butyl hypochlorite (11.8 mg, 0.11 mmol) in 2 ml of methylene chloride while maintaining the temperature at -78°C. The mixture was stirred for greater than 1 h at -78°C and allowed to warm to room temperature with stirring overnight. Analysis of the reaction mixture by injection of an aliquot into a GCms revealed that six products were formed with mass spectra consistent with: two monochlorinated tribenzazepines (with tentative structures **37** and **38**), isomer #1: GC retention time 17.63 min; m/z 279 (M+2, 33%), 277 (M+, 100), 241 (17), 215 (14); isomer #2: GC retention time 20.04 min; m/z 279 (M+2, 34%), 277 (M+, 100), 241 (17), 215 (14); three dichlorinated tribenzazepines (with tentative structures **39**, **40** and **41**), isomer #1: GC retention time 22.39 min; m/z 315 (M+4, 12%), 313 (M+2, 68), 311 (M+, 100), 275 (6), 251 (4), 249 (10), 241 (14), 240 (13), 213 (5); isomer #2: GC retention time 23.42 min; m/z 315 (M+4, 12%), 313 (M+2, 68), 311 (M+, 100), 275 (9), 251 (5), 249 (8), 241 (14), 240 (15), 213 (4); isomer #3: GC retention time 27.83 min; m/z 315 (M+4, 13%), 313 (M+2, 67) 311 (M+, 100), 275 (9), 251 (11), 249 (11), 241 (13) 240 (13); one trichlorinated tribenzazepine (**42**); GC retention time 34.01 min; m/z 349 (M+4, 33%), 347 (M+2, 98), 345 (M+, 100), 309 (6), 285 (7), 283 (7), 275 (13), 240 (9), 238 (10).

Reaction of 9H-Tribenz[b,d,f]azepine (34) with t-Butyl Hypochlorite and with Addition of Methanol.

9H-Tribenz[b,d,f]azepine (**34**) (7 mg, 0.03 mmol) was dissolved in 1 ml of methylene chloride and cooled to -78°C in a flask equipped with a calcium chloride drying tube. To this solution was added dropwise t-butyl hypochlorite (3.1 mg, 0.03 mmol) in 1 ml of methylene chloride while maintaining the temperature at -78°C. The mixture was stirred for 15 min, 2 ml of methanol was added dropwise and stirring was continued for greater than one hour at -78°C and then allowed to warm to room temperature. Analysis of the reaction mixture by GCms revealed the same product mixture that forms in the absence of added methanol (see above).

Reaction of 9H-Tribenz[b,d,f]azepine (34) with Silver Trifluoroacetate.

A solution of 9H-Tribenz[b,d,f]azepine (**34**) (10 mg, 0.041 mmol) in 1 ml of methylene chloride was combined with a solution of silver trifluoroacetate (18 mg, 0.082 mmol) in 1 ml of methanol, refluxed for 20 h and filtered to yield 7.3 mg of silver (83%). The solvent was evaporated from the filtrate and the residue was redissolved in 2 ml of methylene chloride and the organic layer was washed with 2 ml of 1N sodium hydroxide, dried over anhydrous sodium sulfate and evaporated to yield 10 mg of a solid with a ^{1}H nmr and GCms identical to **34**.

ACKNOWLEDGMENT

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