2 Me - HF)$^+$]. Anal. Calcd for $C_{19}H_{39}F$: C, 79.72; H, 13.63. Found: C, 79.93; H, 13.30.

Fluorination of 3,7-dimethyloctyl *p*-nitrobenzoate (51) was carried as described above on 0.5 g (1.6 mmol) using 3% F_2 in N_2. After the usual workup, the crude reaction mixture was flash chromatographed with 3% EtOAc in PE, followed by HPLC using 1% EtOAc in cyclohexane as eluent. The pure **52** was thus isolated in 30% yield: ^{1}H NMR 8.25 (4 H, AB, J = 8 Hz), 4.24 (CH_2O, 2 H, t, J = 6.7 Hz), 1.34 (Me_2CF, 6 H, d, J_{HF} = 19 Hz), 0.99 (CH_3CH, d, J = 6 Hz), 1.8-1.0 (9 H, m); ^{19}F NMR -138.3 (heptet, J_{HF} = 18 Hz); MS, m/e 139 [(M - HF - $OCOC_6H_4NO_2$)$^+$]. Anal. Calcd for $C_{17}H_{24}FNO_4$: C, 62.77; H, 7.38. Found: C, 63.08; H, 7.72.

Acknowledgment. We thank the Fund for Basic Research administrated by the Israel Academy of Science and Humanities for supporting this research.

Registry No. 1, 5911-04-6; **2**, 90304-30-6; **3**, 77894-20-3; **4**, 110318-88-2; **5**, 38120-06-8; **6**, 77894-24-7; **7**, 123-92-2; **8**, 57392-55-9; **16**, 77894-22-5; **17**, 77894-27-0; **19** (alcohol), 4730-22-7; **19**, 928-68-7; **20**, 110318-89-3; **21**, 42842-12-6; **22**, 110330-30-8; **23**, 110318-90-6; **24**, 110318-91-7; **26**, 1617-04-5; **27**, 77894-29-2; **28**, 57392-48-0; **29**, 77894-28-1; **32**, 54576-13-5; **33**, 82953-27-3; **34**, 4751-49-9; **35**, 110318-92-8; **36**, 110318-93-9; **37**, 110318-94-0; **38**, 40065-27-8; **39**, 82953-29-5; **40**, 82953-26-2; **41**, 82953-30-8; **42**, 110318-95-1; **43**, 110318-96-2; **46**, 110318-98-4; **47**, 110318-99-5; **48**, 1921-70-6; **50**, 90304-32-8; **51**, 77894-21-4; **52**, 110319-00-1; MEM chloride, 3970-21-6; $Me_2CHCH_2CH(NH_2)CH_2OH$, 502-32-9; $Me_2CHCH_2CH(NHCOCl_3)CH_2OH$, 110318-97-3; $MeCO(CH_2)_2CHMe_2$, 110-12-3; citronellol, 106-22-9; leucine, 61-90-5.

Novel Synthesis and Spectral Characterization of an *N*-Acetoxyarylamine: *N*-Acetoxy-2,4-dinitrophenylamine

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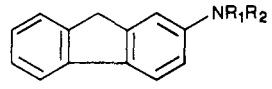
N-Acetoxyarylamines have been proposed as reactive metabolites of carcinogenic aromatic amines. As a model compound to investigate the synthesis and spectral characteristics of these proposed intermediates, stable crystalline *N*-acetoxy-2,4-dinitrophenylamine (**5**) was prepared on condensation of *O*-acetylhydroxylamine with 2,4-dinitrofluorobenzene. Its physical and spectroscopic properties (IR, UV, NMR, MS) were identical with those of the product prepared on acetylation of *N*-hydroxy-2,4-dinitrophenylamine (**6**) with acetic anhydride. The *N*-acetoxy compound **5** could also be prepared by treatment of the hydroxylamine **6** with *p*-nitrophenyl acetate. Under more strenuous acetylating conditions with acetic anhydride the *N,O*-diacetate derivative **8** was produced from the hydroxylamine **6**. The acetylation site in the stable monoacetate derivative differs from that formed on acetylation of other *N*-hydroxyarylamines. The unstable *N*-hydroxy-*N*-acetyl-2,4-dinitrophenylamine was prepared by transesterification of the *N,O*-diacetate **8** with methanol/sodium acetate. Acetic anhydride and *p*-nitrophenyl acetate, under mild conditions, converted *N*-hydroxy-2-aminofluorene to *N*-hydroxy-2-(acetylamino)fluorene and to 2,2'-azoxyfluorene, respectively. *N*-Acetoxy-2-aminofluorene could not be detected in either case.

Introduction

N-Acetoxyarylamines have been proposed as ultimate reactive metabolites of carcinogenic aromatic amines.[1] The mutagenicity of the well-documented carcinogen, 2-(acetylamino)fluorene (**1**) is believed to result from an electrophilic interaction of a putative intermediate, such as *N*-acetoxy-2-aminofluorene (**2**) with DNA.[2] This metabolite is thought to be formed by an enzyme-mediated transacetylation of *N*-hydroxy-2-(acetylamino)fluorene (**3**) a cytochrome P-450 catalyzed oxidative metabolite of 2-(acetylamino)fluorene.[3] *N*-Hydroxyarylamines are also converted to *N*-acetoxyarylamines apparently by acetyl CoA dependent enzymatic O-esterification.[4] Evidence for such a mechanism is based solely on indirect experiments. *N*-Acetoxy-2-aminofluorene has never been synthesized or isolated as a metabolite due to its apparent instability, and attempts to isolate other similar derivatives from metabolic mixtures have not been successful. However, the chemical preparation of a number of *N*-acetoxyarylamines have been reported,[1b,c,5] although only the 4-aminoquinoline 1-oxide derivatives have been fully characterized.[6]

The first synthesis of an *N*-acetoxyarylamine was reported in 1923.[7] In that work *N*-acetoxy-2,4-dinitrophenylamine (**5**) was prepared by the acetylation of *N*-



1, R_1 = $COCH_3$, R_2 = H
2, R_1 = H, R_2 = $OCOCH_3$
3, R_1 = $COCH_3$, R_2 = OH
4, R_1 = $COCH_3$, R_2 = $OCOCH_3$

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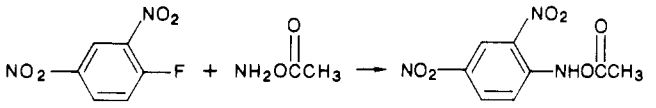
Table I. Infrared Spectral Bands (in cm^{-1}) of 2,4-Dinitrophenylamine and 2-Aminofluorene Derivatives[a]

	$\nu_{N-H,O-H}$	$\nu_{C=O(OAc)}$	$\nu_{amide\ I\ band\ (NAc)}$
2-(acetylamino)fluorene (1)	3285		1650
N-hydroxy-2(acetylamino)fluorene (3)	3250–2800 br		1615[b]
N-acetoxy-2-(acetylamino)fluorene (4)[c]		1790	1690
N-acetoxy-2,4-dinitrophenylamine (5)	3350 sh	1800	
N-hydroxy-2,4-dinitrophenylamine (6)	3440 and 3280		
N-hydroxy-*N*-acetyl-2,4-dinitrophenylamine (7)[d]			1620
N-acetoxy-*N*-acetyl-2,4-dinitrophenylamine (8)		1805	1695[e]

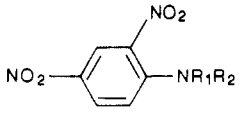
[a] Infrared spectra were recorded in KBr pellets on a Perkin-Elmer Model 727B spectrometer. [b] 1635 cm^{-1} in methanol in CaF_2 cell. [c] The spectrum was also reported by Gutmann and Erickson.[21] [d] Recorded in methanol-d_4 in CaF_2 cells on the 45-min reaction mixture (see Experimental Section). The OH band was obscured by solvent. [e] 1700 cm^{-1} (br) in methanol-d_4 in CaF_2 cell.

Scheme I



5

hydroxy-2,4-dinitrophenylamine (6) using acetic anhydride. The product was characterized solely on the basis of elemental analysis, melting point determination, and chemical reactivities. Thus no definitive differentiation was possible between the proposed structure 5 and its isomer *N*-hydroxy-*N*-acetyl-2,4-dinitrophenylamine (7).

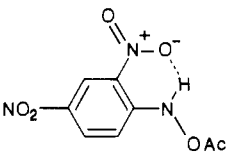


6, R_1 = H, R_2 = OH
7, R_1 = $COCH_3$, R_2 = OH
8, R_1 = $COCH_3$, R_2 = $OCOCH_3$

We describe here the unambiguous synthesis of *N*-acetoxy-2,4-dinitrophenylamine, in which *O*-acetylhydroxylamine is reacted with 2,4-dinitrofluorobenzene. The product of the synthesis is characterized by a range of spectral techniques and is compared with that formed by using the alternate synthetic pathway described by Borsche.[7] Also, an additional procedure for O-acetylation of the arylhydroxylamine 6 has been devised using milder conditions. The application of these procedures to the synthesis of the putative mutagenic metabolite of 2-(acetylamino)fluorene has been investigated.

Results and Discussion

The mild acetylation of *N*-hydroxyarylamines with ketene,[8] acetic anhydride,[9] or acetyl chloride[10] consistently leads to the formation of *N*-hydroxyarylamides. However, an early report of Borsche[7] indicated that under mild conditions *N*-hydroxy-2,4-dinitrophenylamine is only O-acetylated with acetic anhydride. In order to confirm the structure of the acetylated compound we have devised an alternative procedure for the preparation of that product, as shown on Scheme I. This involves the nucleophilic displacement of a labile fluorine substituent in 2,4-dinitrofluorobenzene with *O*-acetylhydroxylamine. *O*-Acetylhydroxylamine was prepared for this purpose as a distilled ethanolic solution, according to the method of Jencks.[11] Its reaction with 2,4-dinitrofluorobenzene progressed under mild conditions in anhydrous ethanol, as monitored by NMR measurements. The essentially pure *N*-acetoxy-2,4-dinitrophenylamine crystallized on cooling from the reaction mixture as shiny yellow moisture-sensitive crystals. In agreement with this structure, the NMR spectrum indicated one acetate group (2.32 ppm) and a 1,2,4-substituted phenyl group. The molecular ion appeared at the expected m/z 241 in the electron impact mass spectrum. The spectrum otherwise exhibited a very minor ketene loss, and a very strong ion formed on loss of AcOH from the molecular ion. The best support for an *N*-acetoxy substituent comes from the infrared spectrum, which exhibits a single strong high-frequency carbonyl absorption band at 1800 cm^{-1} (Table I). For comparison, the related functional groups in an *O*-acetyloxime,[6a] *N*-acetoxy-*p*-nitrobenzoylamide,[12] and compound 4 show carbonyl stretching frequencies at 1805, 1805, and 1790 cm^{-1}, respectively. In contrast an *N*-hydroxyacetamide, such as compound 3, exhibits the amide I stretching band at the lower frequency of 1615 cm^{-1} in KBr pellet. The sharp intense band at 3350 cm^{-1} corresponded to the N–H functionality in compound 5. Acidic character or intramolecular hydrogen bonding, such as shown in structure 5a, is indicated in aprotic solvent by the unusually low-field



5a

chemical shift of the NH proton at 11.25 ppm in the NMR spectrum. We studied the stability of compound 5 under neutral conditions in dry ethanol-d_6 by proton NMR. The loss of acetyl moiety, producing the orange hydroxylamine 6, occurred slowly and greater than 95% of the initial *N*-acetoxyamine remained in solution after 7 days.

Ascertaining the status of the labile acetate group was of importance in the above characterization in that NOAc compounds are known to undergo O to N acyl migration[11,13] or in the case of arylamide derivatives N to ortho carbon migration also.[8,14,15] On the basis of structural analysis of product 5 it is concluded that neither the starting *O*-acetylhydroxylamine nor the *N*-acetoxyarylamine product had undergone such molecular rearrangements.

In an alternate approach the preparation of *N*-hydroxy-2,4-dinitrophenylamine was performed in good yield according to Borsche's procedure.[7] The orange red hydroxylamine was characterized by proton NMR and negative ion FAB mass spectrometry. Acetylation of this hydroxylamine, 6, yielded different products depending upon the conditions used. Mild acetylation with acetic

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anhydride rapidly produced the yellow crystalline monoacetate, which on basis of its physical and spectral characteristics was indeed identical with the N-acetoxyamine **5** characterized above. N-Hydroxy-2,4-dinitrophenylamine could also be monoacetylated to N-acetoxyamine **5** under mild conditions with p-nitrophenyl acetate. This reaction proceeded slowly and compound **5** was the only product.

Acetylation of N-hydroxy-2,4-dinitrophenylamine with acetic anhydride in pyridine resulted in the formation of powdery white crystals, whose melting point was in agreement with that reported earlier for the diacetate derivative.[7] Our spectral data supported the assignment to the N-acetoxyacetamide structure **8**. The mass spectrum provided the expected molecular weight indicating ion at m/z 283. The acyl methyl groups were found as two sharp singlets in the proton NMR spectrum. Again an N-acetoxy functionality was indicated by a high-frequency band in the infrared spectrum at 1805 cm^{-1}. The second acetate was observed as an acetamido functionality as demonstrated by the amide I stretching band at 1695 cm^{-1}. The acetamido group provides the ketene loss from the molecular ion, resulting in the base peak in the mass spectrum of this diacetate derivative. A distinctly different ultraviolet spectrum was observed for the diacetate derivative relative to the monoacetate, with absorption maxima of 290 and 330 nm, respectively. The lower wavelength UV absorption of the N-acetoxyacetamide may be an indication that the two bulky substituents on the nitrogen in the hindered ortho position to the nitro group force the N-acetoxyamido group out of plane of the phenyl ring, thus minimizing the π electron interactions of the trisubstituted nitrogen with the aromatic ring. Such out-of-plane configuration for the amido group in ortho-substituted N-methylacetanilides was observed earlier on basis of NMR and X-ray crystallographic data.[16] Our NMR-monitoring experiments indicate that the diacetate is hydrolyzed in aqueous methanol at room temperature to the O-acetoxyarylamine **5** to the extent of 50% in 8 days. The product in this hydrolysis is expected to have at least a sterically more favorable planar configuration.

The preparation of the N-hydroxy-N-acetyl isomer **7** was achieved by sodium acetate catalyzed transesterification of the N,O-diacetate **8** in anhydrous methanol.[15,17] After 45 min at 50 °C an essentially pure product was obtained showing one new acetate signal at 2.28 ppm and three aromatic protons at chemical shift positions that were distinct from that of the acetoxy derivative **5** in the NMR spectrum. The IR spectrum of the reaction mixture in methanol-d_4 demonstrated the disappearance of the high-frequency acetoxy band at 1805 cm^{-1} as the reaction progressed. The amide band appeared at 1620 cm^{-1}. The latter band compares well with that observed for the authentic N-hydroxyacetamide **3** at 1635 cm^{-1} in methanol (Table I) and for other N-hydroxyphenylamide derivatives.[8] The spectral data, taken together with the molecular weight finding of 241, allowed the structural assignment to compound **7**. This material proved to be unstable. NMR-monitoring indicated that compound **7** in the reaction medium at room temperature is further hydrolyzed to N-hydroxy-2,4-dinitrophenylamine in 4 h in 50% yield. Attempts at aqueous workup of the reaction mixture also yielded mainly the N-hydroxyarylamine **6**.

The N-acetoxyarylamine **5**, prepared here by utilizing three different procedures, comprises the first stable species in its class that has been crystallized and fully

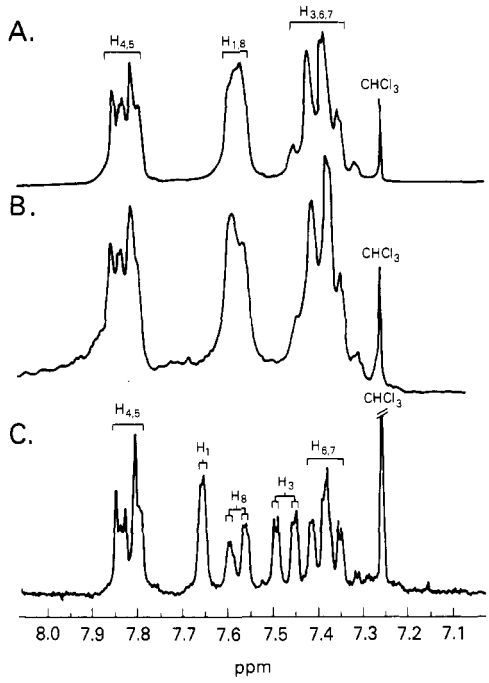

Figure 1. ^1H NMR (200 MHz) spectra at 22 °C in $CDCl_3$, aromatic region only: (A) authentic N-hydroxy-2-(acetylamino)-fluorene (**3**); (B) in situ acetylation product of N-hydroxy-2-aminofluorene with acetic anhydride; (C) authentic N-acetoxy-2-(acetylamino)fluorene (**4**). Chemical shift assignments are according to Evans and Miller.[24] Resonance positions are similar to the trans amide isomers at −50 °C in EtOH-d_6.

characterized. In this instance the electronegative substituents in the aromatic ring stabilize the otherwise labile N–O bond of the acetoxy group. Hydrogen bonding of the N–H to the ortho nitro group also mitigates against the O to N acyl migration of the initially formed monoacetate. O-Acetylation is probably the first step in the acetylation reaction, as Jencks observed that for hydroxylamines in general this is the kinetically favored site.[11] In the case of compound **5** O to N acyl migration would require the out-of-plane rotation of the resulting N-hydroxyacetamide because of steric crowding. Finally, the spectrally characterized derivatives here fully confirm the structural assignments of Borsche[7] on basis of his chemical reactivity studies six decades ago.

Application of the above acetylation conditions to the synthesis of N-acetoxy-2-aminofluorene was not successful. Mild acetylation of N-hydroxy-2-aminofluorene with p-nitrophenyl acetate yielded only 2,2′-azoxyfluorene. The mechanism of this reaction was not investigated further, but presumably the p-nitrophenol reagent induces a radical-catalyzed oxidation to nitrosofluorene, which in turn is converted to the azoxy compound. We reinvestigated the mild acetylation of N-hydroxy-2-aminofluorene with acetic anhydride.[9] The ultimate product isolated previously by others was identified as the N-hydroxyacetamide **3**. In hope of observing the initial product formed, possibly an N-acetoxyamine, we monitored the reaction by NMR (Figure 1), howver, the only product observed was N-hydroxy-2-(acetylamino)fluorene (**3**).

It is recognized that the stable dinitrophenyl derivative **5**, characterized here, is a special case of N-acetoxyarylamines, because of the stabilizing effect of the strongly electronegative ring substituents. There is strong evidence in the recent literature, however, that reactive unstable N-acetoxyarylamines may be important metabolic activation products of mutagenic and/or carcinogenic aromatic amines, such as Glu-P-1,[1c,5b] N,N-dimethyl-4-aminoazo-

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benzene,[1b] Trp-P-2,[18] and others,[4a,19] and that this species reacts with nucleic acids to form adducts. The putative reactive species were generated in these in vitro reactions with acetic anhydride, ketene, or Acetyl CoA dependent acetylase enzyme. Direct proof for the existence of these reactive intermediates will require further studies.

Experimental Section

Melting points were taken on a Unimelt capillary melting point apparatus and were uncorrected. Proton NMR spectra were determined at 200 MHz by using a Varian XL-200 spectrometer with tetramethylsilane as internal standard. UV spectra were recorded on a Gilford Model 2600 spectrophotometer. Mass spectra were obtained on a VG-7070E-HF spectrometer, either in positive electron impact (EI) ionization mode at 70-eV ion energy and solids probe sample inlet or in the positive or negative fast atom bombardment (FAB) ionization mode using xenon bombarding atoms and diethanolamine or dithiothreitol/dithioerythritol (5:1) sample matrices, as specified below. *N*-Hydroxy-2-(acetylamino)fluorene[20] was received from the NCI Chemical Carcinogen Reference Standard Repository, a function of the Division of Cancer Etiology, NCI, NIH, Bethesda, MD 20892. *N*-Acetoxy-2-(acetylamino)fluorene was prepared as reported previously.[21] All other chemical reagents were from standard commercial sources.

***O*-Acetylhydroxylamine.** The method of Jencks[11] was used for the preparation of *O*-acetylhydroxylamine in ethanol. The synthesis was also performed in ethanol-d_6 (99 atom % D, MSD isotopes). A freshly prepared neutralized mixture (250 μL) of aqueous 4 M NH_2OH·HCl and 3.5 M NaOH was added to *p*-nitrophenyl acetate (0.51 mmol) in ethanol-d_6 (5 mL) at 0 °C. The mixture was stirred for 60 min and then distilled under vacuum (15 mmHg) at 35 °C. The distillate (2 mL) was examined by NMR [in CD_3OD, δ 2.05 (s)]. Quantitation of *O*-acetylhydroxylamine produced, performed as described previously,[11] indicated a yield of 0.23 mmol (45%).

Synthesis of *N*-Acetoxy-2,4-dinitrophenylamine (5). 2,4-Dinitrofluorobenzene (18 μmol) in ethanol-d_6 (22.7 μL) was added to *O*-acetylhydroxylamine (9 μmol) in ethanol-d_6 (500 μL) in an NMR tube (5 mm o.d.). NMR spectra were measured at various time points. After 96 h the reaction mixture was cooled at 4 °C overnight, whereupon yellow crystals deposited. The supernatant was removed, and the resulting *N*-acetoxy-2,4-dinitrophenylamine, yield 91%, was redissolved in methanol-d_4 for NMR analysis: δ 2.32 (s, 3, OAc), 7.40 (d, 1, H_6, $J_{5,6}$ = 9.4 Hz), 8.41 (dd, 1, H_5), 9.04 (d, 1, H_3, $J_{3,5}$ = 2.6 Hz). Recrystallization from anhydrous ethanol: mp 160 °C (lit.[7] mp 164 °C); NMR ($CDCl_3$) δ 2.36 (s, 3, OAc), 7.36 (d, 1, H_6, $J_{5,6}$ = 9.3 Hz), 8.41 (dd, 1, H_5), 9.14 (d, 1, H_3, $J_{3,5}$ = 2.6 Hz), 11.29 (br s, 1, NH); MS (EI+), (relative intensity) *m/z* 241 (12, $M^{\cdot+}$), 199 (2, M − C_2H_2O), 183 (12), 181 (100, M − AcOH), 165 (5), 153 (4), 105 (10), 104 (12), 77 (53), 75 (75), 74 (45), 60 (28), 43 (100); infrared absorption bands are given in Table I; UV λ_{max} (EtOH) 257.8 (ε 8900), 329.8 nm (11 100). A trace of moisture in diluent ethanol produced a reddish solution with UV spectrum: λ_{max} (rel A) 398.2 (0.46), 497.8 nm (0.17).

***N*-Hydroxy-2,4-dinitrophenylamine (6).** The method of Borsche[7] was used for the synthesis of **6** from 2,4-dinitroanisole and hydroxylamine in the presence of sodium ethoxide in 63% yield. The orange red product was crystallized from diethyl ether: mp 75 °C (lit.[7] mp 80 °C); NMR (CD_3OD) δ 7.57 (d, 1, H_6, $J_{5,6}$ = 9.6 Hz), 8.32 (dd, 1, H_5), 8.98 (d, 1, H_3, $J_{3,5}$ = 2.6 Hz). MS (FAB−; matrix, DTT/DTE, 5:1) *m/z* (relative intensity) 198 (63, M − H), 182 (100, M − OH), 166 (25, M − OH − O), 138 (4); MS (FAB−; matrix, diethanolamine), *m/z* (relative intensity) 303 (14, M + DEA − H), 287 (5, M + DEA − OH), 271 (3), 258 (3), 198 (100, M − H), 182 (75, M − OH), 166 (21, M − OH − H), 153 (13, M − NO_2), 151 (11, M − NO_2 − H_2), 138 (8); EI(+)MS obsd M^+ 199.0183, calcd for $C_6H_5N_3O_5$ 199.0229; IR (Table I).

Acetylation of *N*-Hydroxy-2,4-dinitrophenylamine. 1. With Acetic Anhydride. According to Borsche's procedure[7] *N*-hydroxy-2,4-dinitrophenylamine (2.5 mmol) was stirred in acetic anhydride (1.89 mL, 20.1 mmol) for 6 h at room temperature. The yellow crystals were filtered under vacuum and washed twice with dry diethyl ether: yield, 89%. The physical and spectral characteristics of this product were identical with those of *N*-acetoxy-2,4-dinitrophenylamine, characterized above.

2. With *p*-Nitrophenyl Acetate. *p*-Nitrophenyl acetate (2.5 mmol) in ethanol (25 mL) was added to a solution of *N*-hydroxy-2,4-dinitrophenylamine (2.5 mmol) in ethanol (20 mL). After the mixture was stirred at room temperature for 6 h the solvent was evaporated with a stream of dry argon to a final volume of 15 mL and then stored at −20 °C for 4 h. The yellow crystals formed were filtered and treated as above: yield, 93%. The physical and spectral characteristics of this product were found to be also identical with those of compound **5**.

3. Diacetylation. A solution of acetic anhydride and pyridine (4:1 v/v; 21.3 mmol of acetic anhydride) was added to *N*-hydroxy-2,4-dinitrophenylamine (2.5 mmol). The mixture was left stirring at room temperature for 4 h, heated to 120 °C for 5 min, and then left to stand at room temperature for 48 h. The mixture initially turned a light brown color, which became darker on heating. A white crystalline product was formed on standing. Ice was added to precipitate more of the crystalline product, *N*-acetoxy-*N*-acetyl-2,4-dinitrophenylamine (**8**), which was filtered off, washed with ethanol, and dried in vacuo: mp 139 °C (lit.[7] mp 141 °C); UV λ_{max} (EtOH) 223.0 (sh, ε 12 500), 289.6 nm (5900); NMR (CD_3OD) δ 2.22 (s, 3, Ac), 2.27 (s, 3, Ac), 7.92 (d, 1, H_6, $J_{5,6}$ = 9.2 Hz), 8.57 (dd, 1, H_5), 8.83 (d, 1, H_3, $J_{3,5}$ = 2.4 Hz); MS (EI+), *m/z* (relative intensity) 283 (36, $M^{\cdot+}$), 241 (100, M − C_2H_2O), 225 (16), 199 (4), 197 (34), 193 (9), 183 (63), 181 (44), 165 (6), 153 (13), 105 (12), 104 (15), 77 (28), 75 (38), 63 (39), 62 (39), 43 (100); IR (Table I). The diacetate **8** in 4% aqueous methanol (D_2O/CD_3OD) at 23 °C decomposed to the *N*-acetoxyarylamine **5** (NMR signals identical with those of compound **5** above) to the extent of 50% in 8 days.

Transesterification of *N*-Acetoxy-*N*-acetyl-2,4-dinitrophenylamine. *N*-Acetyl-*N*-acetoxy-2,4-dinitrophenylamine (69 μmol) and anhydrous sodium acetate (77 μmol) were dissolved in dry CD_3OD (2.2 mL) and heated at 50 °C for 45 min. NMR on the resulting violet solution indicated the presence of an essentially pure product, compound **7**: (CD_3OD) δ 2.28 (s, 3, Ac), 7.29 (d, 1, H_6, $J_{5,6}$ = 9.7 Hz), 8.15 (dd, 1, H_5), 9.00 (d, 1, H_3, $J_{3,5}$ = 2.6 Hz), and 2.02 (s, CD_3OAc, identified with authentic methyl acetate). IR on the reaction mixture showed the following: (in CD_3OD) 1700 (br, CD_3OAc), 1620 (amide), 1570 cm^{-1} (NaOAc). The band at 1805 cm^{-1} disappeared as the reaction progressed. UV λ_{max} (CD_3OD–CH_3OH) (rel A) 217.4 (1.00), 257.0 (0.82), 335.0 (0.63), and 388.0 nm (0.62). MS (EI+) on the reaction mixture evaporated into solids probe, *m/z* (relative intensity) 241 (1, $M^{\cdot+}$), 197 (4, M − ($COCH_3$ + H)), 183 (18), 181(100, M − AcOH), 165 (30) 105 (16), 104 (12), 75 (60). The reaction mixture on further standing for 4 h at 23 °C was converted to the arylhydroxylamine **6**, as observed by NMR: (CD_3OD) δ 7.57 (d), 8.32 (dd), and 8.98 (d), and the methyl acetate singlet increased at δ 2.02. Similarly, workup of the 45-min reaction mixture by solvent evaporation, ethyl acetate dissolution, and washing with aqueous ice cold sodium bicarbonate yielded a mixture of *N*-hydroxyacetamide **7** and arylhydroxylamine **6**.

Acetylation of *N*-Hydroxy-2-aminofluorene. *N*-Hydroxy-2-aminofluorene was synthesized according to published procedures[22] and was further characterized by NMR: (EtOH-d_6) δ 3.79 (s, CH_2), 6.98 (dd, *J* = 8.1 Hz, 2), 7.14 (br t), 7.20 (br s, H_1), 7.26 (br t), 7.43 (d, *J* = 7.3 Hz), 7.59 (d, *J* = 8.3 Hz), 7.63 (d, *J* = 8.1 Hz); MS (EI+), *m/z* (relative intensity) 197 (5, $M^{\cdot+}$), 195 (29), 181 (100, M − O), 180 (67), 165 (69, M − NHOH).[23]

1. With Acetic Anhydride. Acetic anhydride (106 μmol) was added to *N*-hydroxy-2-aminofluorene (20.3 μmol) and $CDCl_3$ (600

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μL) in an NMR tube. The reaction proceeded virtually instantaneously at 22 °C to yield *N*-hydroxy-2-(acetylamino)fluorene (**3**)[24] as monitored by NMR: ($CDCl_3$) δ 2.23 (s, Ac_2O), 2.09 (s, AcOH), 2.14 (s, CH_3CON), 3.94 (s, CH_2) [for aromatic protons see Figure 1, Chart B]; MS (FAB+, glycerol), *m/z* (relative intensity) 240 (69, M + H^+), 224 (100), 223 (55), 196 (9), 181 (50), 180 (26); obsd M + H 240.1080, calcd 240.1025.

2. With *p*-Nitrophenyl Acetate. *p*-Nitrophenyl acetate (8 μmol) in EtOH-d_6 (400 μL) was added to *N*-hydroxy-2-aminofluorene (8 μmol) in the same solvent (400 μL) at 22 °C. Orange-red crystals precipitated, and after 48 h the solid product was isolated and identified as 2,2'-azoxyfluorene:[25] NMR ($CDCl_3$) δ 3.99 (2 H, s, CH_2), 4.03 (2 H, s, CH_2), 7.40 (m), 7.60 (m), 7.86 (m), 8.19 (d), 8.40 (d), 8.52 (s), 8.67 (s); mass spectrum was identical with previously published data.[25]

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Registry No. 1, 53-96-3; 3, 53-95-2; 4, 6098-44-8; 5, 610-53-7; 6, 51348-06-2; 7, 110319-04-5; 8, 110319-05-6; *N*-hydroxy-2-aminofluorene, 53-94-1; *O*-acetylhydroxylamine, 19479-87-9; *p*-nitrophenyl acetate, 830-03-5; 2,4-dinitrofluorobenzene, 70-34-8; 2,4-dinitroanisole, 119-27-7; 2,2'-azoxyfluorene, 15961-88-3.

Sulfuration of the Norbornene Double Bond

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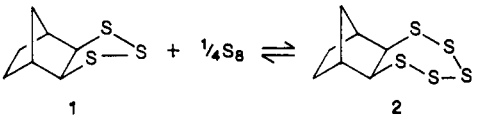
Norbornene reacts with elemental sulfur to give the trithiolane **1** and the pentathiepane **2** in an equilibrium ratio of 3.5:1, the reaction being favored by polar solvents such as dimethylformamide or dimethyl sulfoxide at temperatures as low as 25 °C. Similar sulfuration has been observed with benzonorbornadiene and dicyclopentadiene. Trithiolanes alone are formed in the sulfuration of 2-arylnorbornenes and of benzosesquinorbornenes. The trithiolane from sulfur and isodicyclopentadiene (**9**) is a (2 + 3) adduct derived from the reactive diene tautomer **10**. Norbornadiene is sulfurated to a mixture of five products, including an episulfide, two interbridge disulfides, the "normal" trithiolane, and a 1,6-trisulfide. In all these reactions there is evidence of polar transition states but of no discrete ionic intermediates. The only effect of radical trapping agents is to limit attendant polymerization.

Introduction

The first study of the reaction between norbornene and sulfur was reported in 1969.[1] The only product isolated was the novel *exo*-norbornane trithiolane (**1**), setting norbornene apart from all the acyclic olefins studied in the past. Later Oae and co-workers[2] obtained a similar result by irradiating a solution of norbornene and sulfur. We have extended the study of the sulfur addition[3] to a number of related compounds chosen to reveal the effects of polarity, stereochemistry, double-bond interactions, and solvent on the sulfuration reaction.

Norbornene and Sulfur. Heating a mixture of sulfur and norbornene in dimethylformamide (DMF) or in dimethyl sulfoxide (DMSO) gave two products. The major component could be easily identified as **1** by comparing its NMR and IR spectra with those reported before.[1,2] The minor component could be precipitated as a white solid. A high resolution mass spectral analysis together with a molecular weight determination indicated that five sulfur atoms had added to norbornene. A four-line ^{13}C NMR spectrum showed the molecule to be symmetrical, consistent with the norbornane pentathiepane structure (**2**). In the ^1H NMR spectrum H-2 and H-3 absorb at δ 3.98 and couple with H-7a (w-coupling) with J = 2.0 Hz. It is now accepted[4] that in substituted norbornane systems, an endo proton couples with the anti methylene bridge proton with a coupling constant ca. 2.0 Hz while the exo proton couples with the bridgehead proton with a coupling constant ca. 4.0 Hz, the w-coupling in this case being absent. A characteristic aspect of the ^1H NMR spectra of **1** and **2** is the chemical shift difference of the methylene bridge protons. In **1**, δ(H-7s) − δ(H-7a) = 0.77, whereas in **2**, δ(H-7s) − δ(H-7a) = 0.48. This difference has now been found to exist in all the pairs of trithiolanes and pentathiepanes studied (Table 3, supplementary material).



1 **2**

In a typical sulfuration reaction the reactants were heated at 100 °C in DMF for 6 h; then the products were worked up by ice-water quenching, precipitation, extraction, and liquid chromatography between 0 °C and room temperature. Combined yields of purified trithiolane and pentathiepane ran around 40%, with the trithiolane–pentathiepane ratio never less than 3:1.

The fact that previous workers[1,2] had not obtained **2** suggested that **2** was decomposing to **1** under the distillation conditions (80 °C/0.05 mm) used. Although $CHCl_3$ and CS_2 solutions of **2** are stable for extended periods, a solution of **2** in DMSO or DMF immediately showed the presence of **1**. ^1H NMR spectra of these solutions showed **1** and **2** to be in the same ratio as obtained in the direct sulfuration of norbornene. By removal of the solvent under vacuum followed by careful preparative TLC it is possible

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