ORGANIC NITROSONIUM SALTS.II.[1,2] STABILITY STUDIES AND OXIDATIONS OF SOME INDOLE DERIVATIVES

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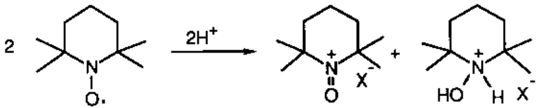
Abstract - The stabilities of various salts of the 2,2,6,6-tetramethylpiperidine-1-oxonium ion were studied. 2,2,6,6-Tetramethylpiperidine-1-oxonium tetrafluoroborate was shown to react with 1,2,3,4-tetrahydrocarbazole (1-H-2,3,4,9-tetrahydrocarbazole) to give, in the presence of water, 4-keto-1,2,3,4-tetrahydrocarbazole in good yield. Under the same conditions, cyclopent[b]indole and cyclohept[b]indole gave the corresponding keto derivatives. In the absence of water, the oxidation of tetrahydrocarbazole gave a mixture of dimers, probably derived from the Diels-Alder self condensation of 1-H-2,3-dihydrocarbazole. The condensation is reversible and, in acid, the dimer mixture gives a salt of 1-H-2,3-dihydrocarbazole which can be reduced with sodium borohydride to give back tetrahydrocarbazole.

Organic nitrosonium salts, easily derived from well known nitroxide radicals[4] by oxidation, are specific oxidizing agents for a number of functional groups. In addition to alcohols, amines, ketones, and benzyl ethers which were reviewed in our previous paper,[2] recent publications record the oxidation of N,N-dialkylanilines[5] and difunctional alcohols[6] as well as the nitrosonium ion catalyzed hypochlorite oxidation of alcohols.[7] In this paper, we would like to report the electrochemical preparation of a nitrosonium salt, studies on the stability of certain nitrosonium salts, and, finally, their reactions with some indole derivatives.

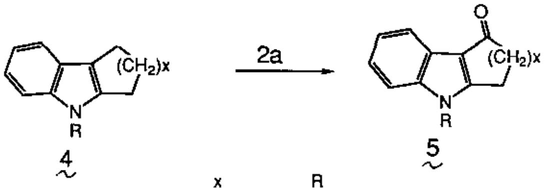
Nitrosonium salts are conveniently prepared from nitroxides by chlorination or bromination (to give nitrosonium chlorides or bromides), by reaction with nitrogen dioxide (to give nitrates), and by acid catalyzed disproportionation (to give salts of the acid used in the reaction, specifically, tetrafluoroborates, perchlorates, and sulfates).[2] We have oxidized commercially available TEMPO (2,2,6,6-tetramethylpiperidinyl-1-oxy), **1**, electrochemically to give the corresponding nitrosonium tetrafluoroborate salt, **2**, in 84% yield. It was, however, more convenient to prepare the nitrosonium salts by the disproportionation method of Golubev, (1→2 + 3) as shown below.[8] Although the disproportionation can yield only 50% of desired salt, efficient methods are available for recovery and recycling of the hydroxyamine, **3**. Using these various methods, we prepared the chloride, the nitrate, the sulfate, the tetrafluoroborate, and the perchlorate salts of **2**. The nitrate and sulfate salts were too hygroscopic to work with. The chloride was also hygroscopic but could be easily isolated. The tetrafluoroborate and perchlorate were only slightly hygroscopic and were stable if kept cold (refrigerator). Although we were never able to detonate the perchlorate, we decided to work exclusively with the tetrafluoroborate rather than risk an accident.



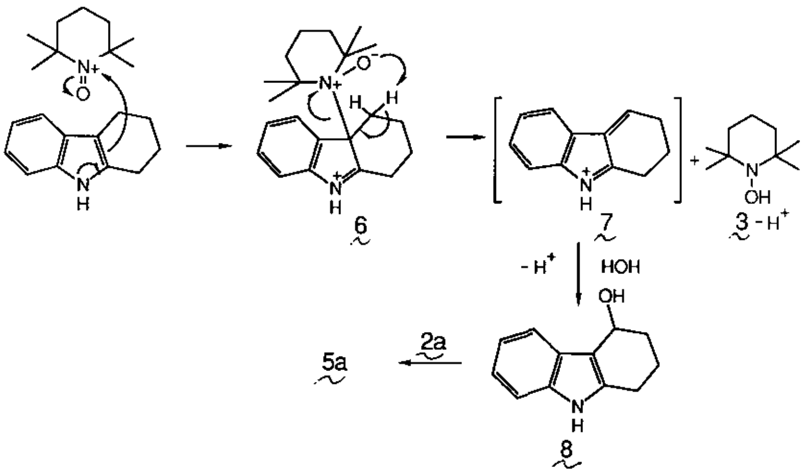
1 **2** **3**

2a, X=BF_4^-
2b, X=ClO_4^-

The cycloalkylindoles, **4a** to **4c**, were oxidized in aqueous CH_3CN to give the keto products, **5a** to **5c**, in yields of 71, 60, and 45%, respectively. The reaction is quite similar to the oxidation of the same indole compounds with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ),[9] a reaction recently used by Cook and his coworkers.[10] When **4d** was oxidized, the corresponding ketone, **5d**, previously unknown, was obtained in 83% yield. A likely mechanism is shown below which involves an initial attack of the indole ring system on the positive nitrogen of the nitrosonium salt to give intermediate **6** which decomposes to give the unsaturated imine, **7**. This imine can react with water to form a 4-hydroxytetrahydrocarbazole, **8**,[11] which is subsequently oxidized to the ketone, **5a**, by a predictable oxidation reaction.[2]



	x	R
a	2	H
b	1	H
c	3	H
d	2	CH_3

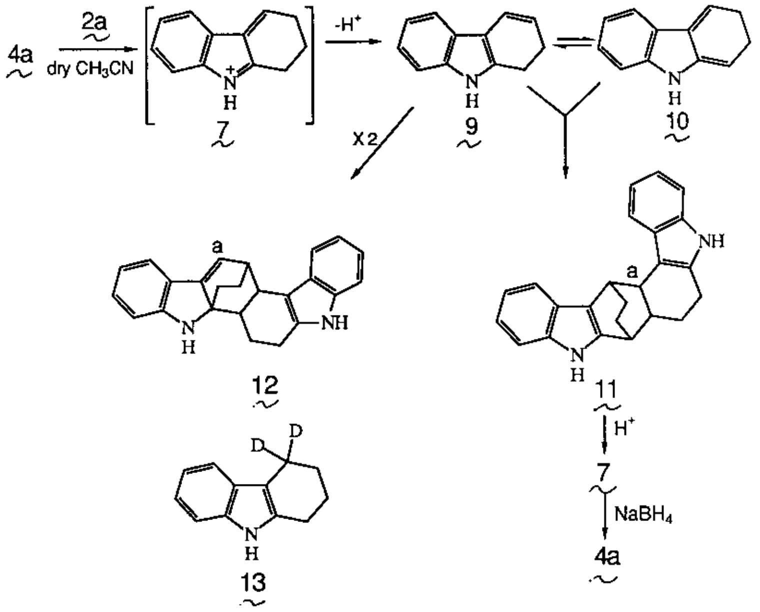


When tetrahydrocarbazole (4a, THC) was treated with 2a in anhydrous CH_3CN, an orange material precipitated in good yield which could be recrystallized, with difficulty, to a white crystalline material with a constant mp of 220-221° C. The material was extremely acid-sensitive (turning blue) but could be recrystallized when a drop of ammonia was added to the solvents. Although the crystallinity and mp would seem to indicate a pure material, the ^{13}C nuclear magnetic resonance spectrum (nmr) had at least 100 peaks, grouped in several narrow areas. A minor product was separated by chromatography which had a mp of 209-211° C. and a similar nmr spectrum. The ultraviolet spectra of both materials were essentially identical to tetrahydrocarbazole, and the aromatic region of the ^{13}C-nmr spectrum was similar in that a group of peaks was present corresponding to each of the aromatic peaks of THC. On this basis, it was concluded that the materials were mixtures of dimers which contained the indole moieties intact. The differences in the ^{13}C-nmr spectra were all in the aliphatic region. THC has all of its aliphatic peaks in a narrow region between 20 and 23 ppm. The aliphatic carbons of the dimeric mixtures appeared in a broad region from 20-50 ppm, again as sets of peaks. The mass spectra, both chemical ionization and a fast atom bombardment, were in best agreement with a dimeric structure, as was a Rast molecular weight. The elemental analysis was close to the calculated value, but the carbon was consistently low. However, the values were close enough to exclude any atoms other than carbon, hydrogen, and nitrogen. On this basis, it appeared that the material corresponded best to a set of isomers derived from a Diels-Alder reaction between two intermediates such as **9** and **10**, which are probably formed from a common intermediate such as **7**, by loss of a proton. One possible isomer is shown as **11**.

Diels-Alder reactions are well known to occur between 3-vinylindoles and several dienophiles.[12] Two types of reaction might occur, one in which two molecules of **9** condense to give a dimer such as **12**, and one in which **9** condenses with **10** to give **11**. In each case, there should be four isomers, corresponding to _endo_ and _exo_ forms where the indole rings are aligned in two different ways to one another. The structure of the dimeric mixture is also supported by the mass spectral fragmentation. Two major peaks correspond to two retro-Diels-Alder reactions; one, to give monomer, **7**, at 170 m/z and a second, loss of 28 units from the molecular ion, corresponding to the two carbon bridge in the structure. All attempts to separate the materials failed. No detailed studies were made on the minor component, although its microanalysis did correspond to a dimeric product.

In an attempt to gain further insight into the structure of **11** or **12**, we prepared the deuterated compound, **13**, by reaction of the corresponding ketone with lithium aluminum deuteride. This compound was oxidized under the conditions used for the preparation of **11**. Unfortunately, the deuterium is distributed in positions corresponding to 1 and 3 of THC by the equilibria shown above, and the mass spectra of the product are useless. However, when the 4,4-dideutero compound, **13**, was oxidized, the product lacked a set of peaks in its ^{13}C-nmr spectrum at 50 ppm. This would correspond to the carbon-hydrogen marked as "a" in **11** and **12**. The shift value of 50 ppm is much more in line with the bicyclo position as in **11** than the vinyl carbon in **12**.

Furthermore, 11 is in better agreement with the general uv and nmr spectra as cited above. The structure of the minor material is even less certain, but is probably similar to that of 11, since the ^{13}C-nmr spectra are similar.



The probability of a Diels-Alder reaction is supported by the fact that acid treatment of 11 seems to reverse the reaction, giving 7 which can be reduced by $NaBH_4$ to give starting material, 4a. Various Diels-Alder reactions of 7 are being studied.

EXPERIMENTAL

General Methods. Melting points were determined on a Kofler Micro hot stage and are corrected. Elemental analyses were carried out by Galbraith Laboratories, Inc., Memphis, Tenn. High resolution mass spectra were measured on a Kratos spectrometer AEI MS-902 with direct inlet at 70 eV and are accurate to + 5 ppm. The fast atom bombardment (FAB) spectra were measured using argon atoms on the sample in a thioglycol matrix on a ZAB H/S spectrometer at Peking University. DADI (Direct Analysis of Daughter Ions) was carried out on a ZAB H/S spectrometer at Peking University. Nuclear magnetic resonance spectra were measured on a Bruker AF-270 spectrometer in the FT mode at 270 mHz.

Deuteriochloroform and deuterated dimethyl sulfoxide were used as solvents, but all shifts are reported in ppm downfield from tetramethylsilane. Thin layer chromatography (tlc) was carried out on silica gel 60 coated plastic sheets from E. Merck. Preparative chromatography was carried out by "flash chromatography"[13] and on a Chromatotron (Model 7924T, Harrison Research Co.).

2,2,6,6-Tetramethylpiperidine-1-oxonium Tetrafluoroborate. a. *By Electrolysis*. The electrolysis was carried out under deoxygenated nitrogen,[14] in a divided cell (Nafion membrane) using a graphite felt anode[15] and a platinum cathode. It was carried out at constant current as controlled by a Princeton Applied Research potentiostat/galvanostat, Model 363, and a standard calomel electrode. Compound **1** (1.04 g) in 100 ml of electrolyte (0.1 M $LiBF_4$ in CH_3CN:H_2O, 9:1) was electrolyzed at a constant current of 80 mA. The initial potential was 0.55 V but increased slowly to 0.67 V and to 0.75 V when the reaction was complete (about 2 h). Tlc (CH_3CH_2OAc:hexane, 3:7) showed the reaction to be complete. The reaction mixture was placed in a freezer overnight during which time, most of the water froze. The supernatant liquid was decanted from the ice and evaporated to dryness on a rotary vacuum evaporator, keeping the external temperature below 80° C. The residual crystals were washed with cold, dry CH_3CH_2OAc to yield 1.35 g (84%) of **2**, mp 162-163°C., lit.[8] 162.5-163.5° C. (dec.). Most of the lithium ion had passed through the membrane and precipitated on the cathode as LiOH; the remainder was apparently removed in the ice decantation.

b. *By Disproportionation*.[8,16] Tetrafluoroboric acid (9 ml of 48% aqueous, 0.06 mol) was added, with stirring, and dropwise, to 5.0 g (0.032 mol) of **1** dissolved in 20 ml of ether in an ice bath. The solution warmed to 15° C, and a yellow precipitate formed. After 10 min, the precipitate was collected by filtration and dried in a vacuum desiccator to yield 3.48 g of **2** (89%), mp 164-165°C. The filtrate was made basic with aqueous ammonia to pH 10, whereupon the layers separated. The layers were separated, and the aqueous layer was extracted with five 15-ml portions of ether. The combined ether layers were concentrated to 3-5 ml and placed in a hood in an open flask so that the hydroxyamine, **3**, could air oxidize back to **1**. After three weeks, the residue solidified to give **1**, 1.95 g (78%), identical with an authentic sample of **1**.

The perchlorate, mp 156-157°, lit.[8] 157-158° C, was prepared in 91% yield by a similar procedure.

Stability Studies. Samples of the perchlorate, the tetrafluoroborate and the chloride[17] were left (a) open and closed to the atmosphere at room temperature, (b) open and closed in a desiccator at room temperature and, (c) closed in a refrigerator. At periodic intervals, the samples were examined by mp, uv spectroscopy, and by titration with thiosulfate, according to Golubev.[18] The open sample of chloride liquified in a few days, but the closed samples were stable for a few weeks. All of the perchlorate and tetrafluoroborate samples at room temperature had gradually falling melting points and shifting uv spectra over a twelve month period. The refrigerated samples of perchlorate and tetrafluoroborate had constant melting points for one year. although the thiosulfate titrations showed a lowered activity of about 10%. The refrigerated tetrafluoroborate had a constant uv spectrum over one year, but the perchlorate changed slightly.

Oxidation of 4a, 4b, 4c, and 4d in Aqueous CH_3CN. A solution of 4a (0.50 g, 2.92 mmol) in 30 ml of $CH_3CN:H_2O$ (9:1) was added dropwise to 1.42 g (5.84 mmol) of 2a in 30 ml of the same solvent. The mixture was stirred one h and evaporated to 5-10 ml, whereupon 5a, (0.20 g) precipitated. The precipitate was collected by filtration, and the filtrate was diluted with H_2O (5 ml) and extracted with five 15-ml portions of ether. The ether solution was dried (sat. aqueous NaCl and Na_2SO_4), evaporated and chromatographed over an alumina column with CH_3CH_2OAc as eluant. The fractions containing 5a were combined, evaporated, and, along with the precipitate, recrystallized from 95% CH_3CH_2OH to give 0.38 g, (71%) of 5a, mp 219-220° C, lit.[9] 219-221° C. A similar reaction carried out with the nitrosonium perchlorate gave a 79% yield of product.

The oxidation of cyclopent[b]indole, 4b[19] with 2a gave a 60% yield of 5b, mp 251-252° C., lit.[9] 252-253° C.

The oxidation of cyclohept[b]indole, 4c[20] with 2a gave a 45% yield of 5c, mp 219-220° C., lit.[9] 220-221° C.

A similar experiment starting with N-methyltetrahydrocarbazole, 4d,[21] gave an

83% yield of 5d, mp 187-188° C. Anal. Calcd for $C_{13}H_{13}NO$: C, 78.39; H, 6.54; N, 7.04. Found: C, 78.15; H, 6.53; N, 7.04.

The byproduct, 3, was recovered from the aqueous layer (by ether extraction) and reconverted to 1 by the procedure given above. Yields were 60-70%.

Oxidation of 4a in Anhydrous CH_3CN. The glassware was oven and fire dried before use, and the experiment was carried out under deoxygenated nitrogen. A solution of 2.75 g (11.3 mmol) of 2a in 10 ml of dry CH_3CN (distilled from phosphorus pentoxide and stored over molecular sieve 3A) was added, dropwise, to an ice-bath cooled and stirred solution of 1.92 g (11.3 mmol of 4a in 15 ml of dry CH_3CN. An orange precipitate started to form after one-fourth of the nitrosonium salt had been added. After half of the salt was added, the precipitate was filtered to give an orange solid. This solid, when washed with cold dry CH_3CN and, subsequently, a few drops of concentrated aqueous ammonia, turned white. It contained only one material (tlc using hexane:CH_3CH_2OAc, 1:1). After the rest of the salt solution was added, the mixture was filtered again to give a purple precipitate which showed two components, one the same as above and a minor material of lower R_F. The combined products were dissolved in CH_3CH_2OAc and deposited on silica gel. This was placed on a column of silica gel and developed with hexane:CH_3CH_2OAc, 7:3. The appropriate fractions were combined, evaporated to dryness, and recrystallized from acetone (very soluble) and 95 % CH_3CH_2OH (almost insoluble). In each recrystallization, a drop of aqueous ammonia was added. The crude precipitate obtained in the first case could also be recrystallized in this manner. The yield of the major component was 1.13 g (59 %), mp 220-221°C. Ms (m/z): EI, 338 (M^+), 310 (M^+ - 28), 168 (base peak), 143; FAB, 339 (M^+ +1), 677 ($2M^+$ + 1), 1015 ($3M^+$ + 1), 170 (M^+ + 1 - 169); DADI, 338 (M^+), 310 (M^+ - 28), 170 (M^+ - 168). ^{13}C Nmr (deuterated DMSO), clusters of peaks, centered at the values given; 22, 30, 40 (as seen in $CDCl_3$, but covered by DMSO), 50, 108, 122, 116, 120, 126, 137. Uv (CH_3CN) λ_{max} (nm, log ϵ) 286 (4.15), 227.8 (4.72). Anal. Calcd for $C_{24}H_{22}N_2$: C, 85.2; H, 6.51; N, 8.28. Found: C, 83.39; H, 6.95; N, 8.40 (using a Thermolite ignition catalyst). Rast molecular weight in camphor: Calcd 338. Found: 400.

The yield of minor component was 0.25 g (13%), mp 209-211° C. Anal. Found: C, 85.46; H, 6.74; N, 8.10. The spectra were essentially identical with those of the major component.

When the major component (10 mg) in 5 ml of CH_3CN was treated with three drops of conc. HCl, the solution turned blue. To the blue solution was added 20 mg of $NaBH_4$ in 1 ml of CH_3OH. The mixture was hydrolyzed with water and extracted with ether. The ether solution was shown to contain almost entirely tetrahydrocarbazole by tlc and gc-ms, by direct comparison with the known material.

4,4-Dideuterotetrahydrocarbazole, **13**. Compound **5a** (370 mg) in 60 ml of dry tetrahydrofuran was added to a suspension of 336 mg of $LiAlD_4$ in 40 ml of the same solvent. After 24 h, the mixture was concentrated under vacuum to about 10 ml and hydrolyzed with 6 ml of 10% KOH and 10 ml of H_2O. Extraction with CH_2Cl_2 followed by drying of the organic solvent (Na_2SO_4) and evaporation to dryness gave 318 mg (92%) of product, mp 119-121° C. Ms (m/z) Calcd for $C_{12}H_{11}ND_2$, 173.1174. Found: 173.1178. The ^{1}H-nmr spectrum of tetrahydrocarbazole shows one peak at 2.7 ppm for the protons on carbons 1 and 4. In the spectrum of **13**, the integral of this peak was reduced by half as predicted.

Oxidation of **13** under the conditions described above gave a deuterated **11** which lacked the cluster of peaks at 50 ppm in its ^{13}C-nmr spectrum.

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REFERENCES AND NOTES

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chemist, a great teacher and a good friend.

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