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NEW FUNCTIONAL GROUP COMBINATIONS IN MEDIUM RINGS. 3°-AMINE SALT WITH SULFOXIDE (1).

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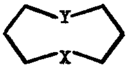
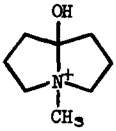
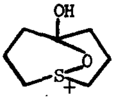
Unusual combinations of functionality have been constructed by incorporating electron-donating and electron-accepting groups in eight-membered rings (I), on opposite sides of the ring but potentially in close proximity, and by then treating the medium-ring compound with a protonic acid to effect transannular bond formation. As representative examples, the perchlorate salts of 1-methyl-1-azacyclooctan-5-one (I, X = CH_3N, Y = CO) and 1-thiacyclooctan-5-one-1-oxide (I, X = SO, Y = CO) were found to exist as the bicyclic structures II and III (2-4). As part of a study of compounds of type I in which the reactive groups X and Y consist of atoms other than carbon (5), we wish to report the synthesis of 5-methyl-1-thia-5-azacyclooctane-1-oxide (I, X = CH_3N, Y = SO), while the attendant Communication from this Laboratory (6) provides proof of the unusual structure of its protonic salt by means of single crystal X-ray analysis.



I

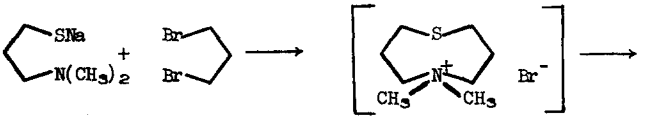


II ClO_4^-



III ClO_4^-

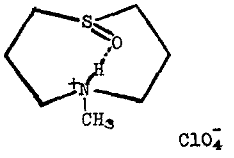
Simultaneous addition of ethanolic solutions containing the sodium salt (IV) of 3-dimethylaminopropanethiol (7) and 1,3-dibromopropane to a large volume of solvent under high dilution conditions (8) gave, in addition to high molecular weight material, a mixture of salts. On the assumption that the salt mixture contained 5,5-dimethyl-1-thia-5-azoniacyclooctane bromide (V) and 1-(3'-dimethylaminopropyl)-1-thioniacyclobutane, since infrared absorption in the region 1600-2600 cm.$^{-1}$ was absent, we subjected the mixture directly to lithium aluminum hydride reduction (9, 10). The two basic products obtained were separated by gas-liquid chromatography (20% Carbowax on firebrick) and redistilled from sodium: (1) 5-methyl-1-thia-5-azacyclooctane, $C_7H_{15}NS$ (11), b.p. 91-92° (25 mm.), n_D^{25} 1.5099, $\lambda_{max}^{C_6H_{12}}$ 212 mμ (ε 3800), yield 13%; perchlorate salt, m.p. 105-106°, ν_{max}^{Nujol} 3120 cm.$^{-1}$ ($\overset{+}{N}$—H); and (2) propyl 3-dimethylaminopropyl sulfide, $C_8H_{19}NS$ (12). Oxidation of 5-methyl-1-thia-5-azacyclooctane with sodium metaperiodate in cold, aqueous solution (13) produced the desired 5-methyl-1-thia-5-azacyclooctane-1-oxide (I, X = CH_3N, Y = SO), $C_7H_{15}NOS$, m.p. 70-72°, ν_{max} 1025 (5% in C_6H_{12}), 1015 (CCl_4), 980 cm.$^{-1}$ ($CHCl_3$) (lower S=O stretching frequency than in all models: thiacyclooctane-1-oxide, methyl 3-dimethylaminopropyl sulfoxide, 4-methylthiamorpholine-1-oxide) (14); $\lambda_{max}^{C_6H_{12}}$ 211 (ε 5000) and ~225 mμ (ε 3800), dipole moment 5.26 (C_6H_6) (15).



IV

I
(X = CH_3N
Y = S)

The perchlorate salt was obtained from 5-methyl-1-thia-5-azacyclooctane-1-oxide in 93% yield, $C_7H_{16}ClNO_5S$, m.p. 126-127°, from which the original amine-sulfoxide could be regenerated by treatment with sodium hydroxide. The perchlorate was also formed by direct oxidation of 5-methyl-1-thia-5-azacyclooctane perchlorate with sodium metaperiodate. A study of the infrared and n.m.r. spectra indicated that in 5-methyl-1-thia-5-azacyclooctane-1-oxide perchlorate the proton is attached to nitrogen (thus ruling out a structure like II with S in place of C-5), as it is in the nitrate salt, $C_7H_{16}N_2O_4S$, m.p. 146-147°. Specifically, the infrared spectra of the solid perchlorate and nitrate exhibited stretching maxima at 2320(m) and 2380(m) cm.$^{-1}$, respectively, far below the frequency region (3030-3150 cm.$^{-1}$) for tertiary amine perchlorates (16), and lower than the broader absorption shown by models, dimethyl sulfoxide + triethylamine perchlorate (2659(s), sh 2460 cm.$^{-1}$ (m)), methyl 3-dimethylaminopropyl sulfoxide perchlorate (2700(s), sh 2510(m), sh 2460(w)), and 4-methyl-thiamorpholine-1-oxide perchlorate (2700(s), sh 2480(m), sh 2360(w)), in which intermolecular hydrogen-bonding can occur ($\overset{+}{N}$—H---O═S). The nitrate salt formed from DNO_3 exhibited an infrared band at 1920 cm.$^{-1}$ which reverted to 2380 cm.$^{-1}$ on recrystallization from a solvent that permitted hydrogen exchange. It was thereby confirmed that the latter band is due to vibration involving hydrogen, and the sum of the infrared data suggested that the hydrogen is very strongly bonded between nitrogen and sulfoxide oxygen. Intermolecular (17, 18) and strong intramolecular (19) O—H---O═S bonding have been observed previously, and this would be an unusual example of the $\overset{+}{N}$—H counterpart. In the n.m.r. spectra as determined in trifluoroacetic acid solution both the perchlorate and nitrate exhibited doublet signals for the methyl protons at τ 6.86 (3H, J = ca. 4.7 c.p.s.) indicative of the attachment of hydrogen to nitrogen, with limited proton exchange. In deuterium oxide, corresponding singlets were observed at τ 7.00 ± .01. The combined infrared and n.m.r. spectral data can thus be accounted for in terms of a perchlorate salt structure in which there is intramolecular hydrogen bonding (VI) or one in which extensive intermolecular bonding between molecules is operative (14). A final decision has not been possible until the X-ray data were



VI

obtained (6) and these provide the first example of $N-H-O_S$ bonding across a ring to form a bicyclic system, as well as the first example of a BC conformation (in the crystal) of an eight-membered ring (20-22).

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(1) Support of this work by research grants (NSF-G14121 and GP2012) from the National Science Foundation is gratefully acknowledged.

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(4) Functional combinations of type II and III have not been observed in open-chain analogs with the reactive groups separated by three methylenic carbons, nor have they been realized in reactions between separate molecules possessing the reactive groups.

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