BICYCLIC PEROXIDES FROM A 1,4-DIAZEPINE

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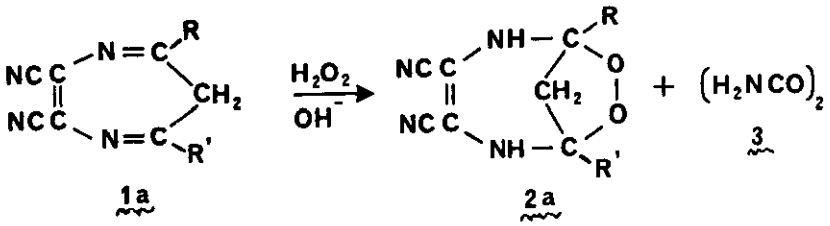
Abstract - An adduct, 3,4-dicyano-1,6-dimethyl-2,5-diaza-7,8-dioxabicyclo[4.2.1]non-3-ene, was obtained from 2,3-dicyano-5,7-dimethyl-6H-1,4-diazepine and hydrogen peroxide in the presence of alkali or a tertiary amine. It was dehydrogenated by iodobenzene diacetate into 3,4-dicyano-1,6-dimethyl-2,5-diaza-7,8-dioxabicyclo[4.2.1]nona-2,4-diene; further oxidation by m-chloroperbenzoic acid gave 4,5-dicyano-1,8-dimethyl-2,7-diaza-3,6,9,10-tetraoxatetracyclo[6.2.1.$0^{2,4}0^{5,7}$]undecane.

Hydrogen peroxide in the presence of sodium hydroxide or pyridine in methanol, or hydrogen peroxide in acetonitrile efficiently transformed 2,3-dicyano-5,7-dimethyl-6H-1,4-diazepine 1a[1] into 3,4-dicyano-1,6-dimethyl-2,5-diaza-7,8-dioxabicyclo-[4.2.1]-non-3-ene 2a,[2] the first example of a bicyclic peroxide from a diazepine. Oxamide was a minor by product. In the absence of an alkali or an amine the reaction in methanol gave traces of the adduct 2a and larger amounts of oxamide and 2,4-pentanedione. Peracids, e.g., m-chloroperbenzoic(MCPBA) or trifluoroperacetic acids, either failed to react with the diazepine 1a under mild conditions or gave intractable mixtures under more severe conditions. The detection of an isocyanide odor during peroxidation of diazepine 1a is being investigated.



1a → 2a + 3

a, R = R' = CH_3; b, R = R' = C_6H_5; c, R = C_6H_5, R' = CH_3

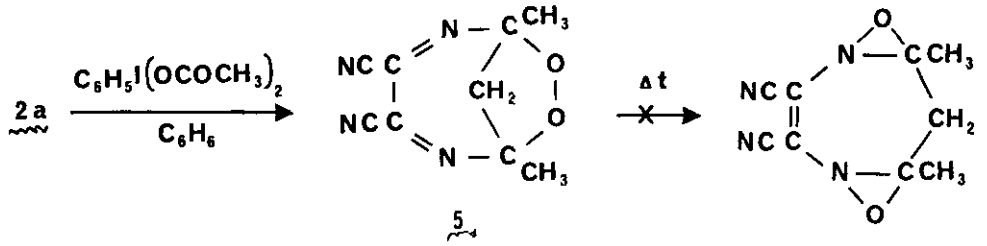
Anticipated reactions between a hydroperoxide and a diazepine apparently did not occur since neither an oxaziridine,[3-5] a nitrone,[3] an amide (other than oxamide),[6] simple ring cleavage,[7] nor ring contraction[8] was detected. The formation of oxamide 3, was attributed to the hydration of cyanogen,[9] a degradation intermediate, by aqueous peroxide. Attempts to obtain peroxides 2b,c from diazepines 1b,c, and to obtain 2,3-dicyano-5,6,6,7-tetramethyl-6H-1,4-diazepine from 3,3-dimethylpentane-2,4-dione and diaminomaleonitrile by an adaptation of the preparation of the azepine 1a[1] were unsuccessful.

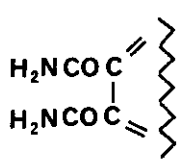
The peroxide structure 2a was directly supported by ir spectroscopic detection of NH, C≡N and C=C functions, by ^{1}H and ^{13}Cnmr detection of methyl and methylene protons and carbon atoms in CH_3, CH_2, CO and CN functions; by molecular weight determination and by elemental analysis. On standing in methanol(25°C, 90 hours), or on heating neat above 125°C (dec) the peroxide 2a fragmented into 2,4-pentanedione and presumably diiminosuccinonitrile 4, a precursor to cyanogen and oxamide 3. The latter was also obtained(47%) from the cyclic peroxide 2a and hydrogen peroxide in methanol (25°C, two days). Triphenylphosphine converted the peroxide 2a into the diazepine 1a.

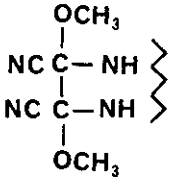
$$(CH_3CO)_2CH_2 + \underset{\underline{4}}{\left[(HN{=}C(CN))_2\right]} \xleftarrow{\Delta t} \underset{\sim}{2a} \xrightarrow{(C_6H_5)_3P} \underset{\sim}{1a} + (C_6H_5)_3PO$$

$$\underset{\sim}{2a} \xrightarrow[25^{\circ}C,\ 48\ h]{\substack{CH_3OH \\ H_2O_2}} \left[\underset{\sim}{4} \xrightarrow{-2\ HCN} (CN)_2\right] \xrightarrow[H_2O_2]{H_2O} \underset{\sim}{3}$$

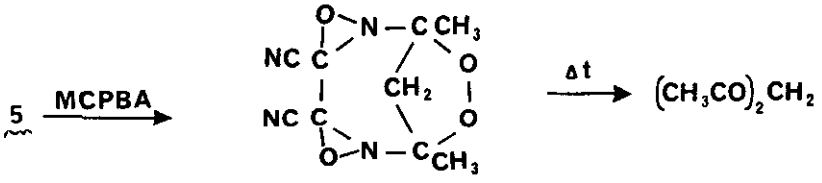
Iodobenzene diacetate in benzene quantitatively dehydrogenated the peroxide 2a into 3,4-dicyano-1,6-dimethyl-2,5-diaza-7,8-dioxabicyclo[4.2.1]nona-2,4-diene 5 (see Experimental Section for confirmation data). Without a trace of isomerization into a bisoxaziridine 6, thermolysis again gave 2,4-pentanedione but the remaining mixture was intractable. During chromatographic separation from silica gel hydration of the dicyanide 5 gave the diamide 7, whereas an azomethine adduct 8 was obtained from methanol containing sulfuric acid. The diazepine 1a was produced in small amounts from the peroxide 5 and triphenylphosphine.

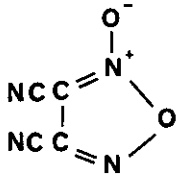


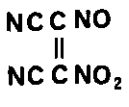


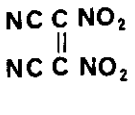


m-Chloroperbenzoic acid(MCPBA) converted the bisimine 5 into 4,5-dicyano-1,8-dimethyl-2,7-diaza-3,6,9,10-tetraoxatetracyclo[6.2.1.$0^{2,4}0^{5,7}$] undecane 9 in moderate yield. The assigned structure was supported by spectroscopic and other analytical data (see Experimental Section). Thermolysis gave 2,4-pentanedione and intractable material. Neither an epoxide of the olefin 6[10] nor dicyanofuroxan 10, an expected fragmentation product, was detected.









Intractable mixtures were obtained from the bisoxaziridine 9 by thermolysis and by further treatment with peroxides. The formation of either a nitrosonitro- 11 or a dinitromaleonitrile 12 was not established. Triphenylphosphine deoxy-

genated the cyclic peroxide 9 into the diazepine 1 in small amounts.

Acknowledgements: Financial support from O.N.R. FD mass spectra from the School of Chemical Sciences, University of Illinois, Urbana, Illinois.

Experimental

Instruments included Perkin Elmer 237B and 521 grating i.r.; Varian A-60 n.m.r.; and Varian MAT 731 FD mass spectrometer. Selected m/e(70 eV) values and all FD values are reported. Each yield was based on starting material consumed. Elemental analyses were provided by Micro-Tech Laboratories, Skokie, Illinois.

Preparation of the diazepine 1a: A condensation between diaminomaleonitrile and 2,4-pentanedione gave the diazepine, mp 202-204°C (dec); ^{1} ^{13}Cnmr ($(CD_3)_2SO$): δ 26.2 (CH_3), 49.4(CH_2), 115.3(C≡N), 122.9(C=C) and 158.3(C=N).

Preparation of the cyclic peroxide 2a: To an ice-cooled stirred suspension of the diazepine 1a (8.0g,46.5 mmoles) in methanol(100 ml) was added a few drops of 1 N sodium hydroxide solution followed by dropwise addition of 90 percent hydrogen peroxide (2.8 ml,100 mmoles). The mixture was stirred until the disappearance (about 3 h) of the diazepine 1a (tlc) left a clear yellow solution. The reaction mixture was concentrated at a temperature below 45°C until a crystalline solid 2a appeared. Dilution with ice-water brought further separation of the peroxide 2a as a light yellow solid which was filtered and dried at room temperature, 7.2g(75%), mp 125-6°C(dec) (ethyl acetate and hexane); ir(KBr):3333(NH), 2222(CN), 1634(C=C) cm^{-1}; ^{1}H-nmr (acetone-d_6): δ 1.68 (s), 2.5-3.2 (m) and 6.57 (br), (D_2O): δ 1.68 (s,6H), and 2.53-3.05 (2H, AB quartet, J = 12 Hz); ^{13}C-nmr (acetone-d_6): δ 23.90 (CH_3), 57.57 (CH_2), 94.40 (C-O), 105.49 (C=C) and 116.95 (CN); m/e (70 eV) (%):206(6) (M^+), 100(100), 85(100); m/e(FD): 206(100)M^+; found: C, 52.08; H, 4.85; N, 27.03 %; $C_9H_{10}N_4O_2$ requires C, 52.42; H, 4.85; N, 27.18 %.

Efficient cooling during slow addition of the hydrogen peroxide to the diazepine 1a controlled an otherwise violent reaction and prevented the formation of oxamide. Both higher temperatures and complete evaporation of the solvent in the rotary evaporator led to product decomposition. The peroxide 2a was stable on refrigeration but exposure to the atmosphere or storage at room temperature brought about blackening and apparent polymerization. The peroxide was also produced (80%) in acetonitrile at room temperature for 17 hours. In methanol the

formation of oxamide predominated on prolonged reaction time, with or without added pyridine. After the peroxide 2a in methanol was stirred at room temperature for 90 hours, 2,4-pentanedione but not the peroxide 2a was detected (tlc).

Treatment of the peroxide 2a (100 mg, 0.5 mmol) with hydrogen peroxide (90%,0.8 ml) in methanol at room temperature for 20 hours gave oxamide (47%), 2,4-pentanedione (tlc) and the odor of an isocyanide.

To a solution of triphenylphosphine (700 mg, 2.7 mmoles) in benzene (25 ml) the peroxide 2a (500 mg, 2.5mmoles) was added and the mixture stirred for 17 hours. The separated colorless solid was filtered and washed with benzene and was identified (tlc) as the diazepine 1a (300 mg, 72 %), mp and mixture mp 201-3°C.

Preparation of the bisimine 5: To a stirred suspension of iodobenzenediacetate (4.0 g, 12 mmoles) in benzene (100 ml) the cyclic peroxide 2a (2.0 g, 10 mmoles) was added in portions. The reaction mixture was stirred for 64 hours at room temperature and filtered to remove unidentified solid material (90 mg). The filtrate on concentration and addition of hexane gave the bisimine 5 as a light yellow solid, 1.7 g(85 %), mp 161-3°C (ethyl acetate and hexane), dec around 170°C; ir ($CHCl_3$): 2230 (CN), 1628, 1588 cm^{-1}; ^{1}H-nmr($CDCl_3$-acetone-d_6): δ 1.86(s, 6H, $2CH_3$) and 3.20(s, 2H, CH_2); ^{13}C-nmr($CDCl_3$-DMSO-d_6): 23.24 (CH_3), 50.93 (CH_2), 96.58 (C-O), 114.75 (CN), and 136.62 ppm (C=N); m/e (70 eV) (%); 172(52), 163(7), 131(100), 100(15), 91(85); m/e (FD): 204(100)M^+, 172(90), 163(10) and 100(10); found: C, 52.67; H, 4.05; N, 26.86; O, 16.69; $C_9H_8N_4O_2$ requires: C, 52.94; H, 3.95; N, 27.44; O, 15.67 %.

Preparation of the bisepoxide 9: To a stirred suspension of m-chloroperbenzoic acid (2.2 g, 12.8 mmoles) in acetone (100 ml) the bisimine 5 (980 mg, 4.8 mmoles) was added in portions at room temperature. The reaction mixture was stirred for 3 hours and concentrated. The residue was dissolved in ethyl acetate, washed with aqueous sodium bicarbonate solution and dried ($MgSO_4$). Removal of solvent furnished a solid (1.0 g) which showed three tlc spots. Chromatography over a silica gel column (25 x 2 cm) gave di-(m-chlorobenzoyl)peroxide, mp 118-120°C(dec)(lit.[11] mp 122-3°C), 80 mg, also obtained from a sample of MCPBA on elution with a mixture of chloroform and hexane (1:9). Elution with a 3:7 mixture of chloroform and hexane gave the bisoxaziridine 9 (200 mg, 17.7 %) as a colorless solid, mp 117-8°C(chloroform-hexane); 140-145°C (dec); ir (CH_2Cl_2): 2245 cm^{-1}

(CN); ^{1}H-nmr ($CDCl_3$); δ 1,72 (s,3H), 1.83 (s,3H) and 2.50-3.15 (AB quartet, 2H, J = 15 Hz); ^{13}C-nmr ($CDCl_3$): δ 20.11 (CH_3), 25.07 (CH_3), 49.31 (CH_2); 74.97 (C-CN) 97.17 (CH_3CO) and 101.88 (CN); m/e (70 eV) (%): 204(1), 100(100); m/e (FD): 237 (100)(MH^+), 186(23), 100(85); found: C, 45.79; H, 3.40; N, 23.85; $C_9H_8N_4O_4$ requires C, 45.77; H, 3.41; N, 23.72%.

Elution with chloroform gave a semisolid (360 mg) which on trituration with a mixture of ethyl acetate and hexane gave a colorless solid, mp 147-9°C (dec) (chloroform-hexane); found: C, 45.17 and 45.22; H, 4.23 and 4.26; N, 19.88 and 19.65; $C_8H_9N_3O_4$ requires: C, 45.50; H, 4.30; N, 19.90 %. It has tentatively been identified as 4-cyano-1,8-dimethyl-2,7-diaza-3,6,9,10-tetraoxatetracyclo[6.2.1. $O^{2,4}$ $O^{5,7}$]undecane, cf. 9 with one cyano group replaced by hydrogen, and will be further investigated.

Preparation of the methanol adduct 8: The bisimine peroxide 5 (100 mg) was dissolved in methanol (5 ml) and a drop of dilute sulfuric acid added. A colorless solid started to separate gradually. After stirring for 17 hours, the reaction mixture was concentrated, diluted with water and filtered to isolate the bis methanol adduct 8 as a colorless solid; 70 mg (52 %); mp 188-190°C (dec) (methanol); ir (KBr): 3330, 2230, 1520, 1495 cm^{-1}; ^{1}H-nmr (DMSO-d_6); δ 3.36 and 3.41 (2 s,6H), 5.6 and 5.7 (2 broad s, 2H, exchanged with D_2O), 2.2-3.0 (AB quartet partly hidden in DMSO peaks, J = 12.5 Hz) and 1.4 (s,6H); m/e (70 eV) (%): 236(18), 235(100), 100(80), 85(100); m/e(FD): 268(100)M^+, 236(10), 235(34) and 98(12); found: C, 49.06; H, 5.95; N, 20.77; $C_{11}H_{16}N_4O_4$ requires C, 49.25; H, 6.01; N, 20.88 %.

A solution of the bisimine 5 (400 mg, 2 mmoles) in benzene (50 ml) was treated with triphenylphosphine (1.05 g, 4 mmoles) added in portions. The reaction mixture turned red-brown. A solid which separated over several hours with stirring was triturated with benzene and ethanol to give the diazepine (tlc) 1a, mp and mixture mp 200-202°C.

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Received, 25th April, 1981