Peroxides. Spiro[cyclohexane-1',3-9-carbamyl-3(*H*)-5,6,7,8-tetrahydrobenzo-1,2,4-dioxazines]

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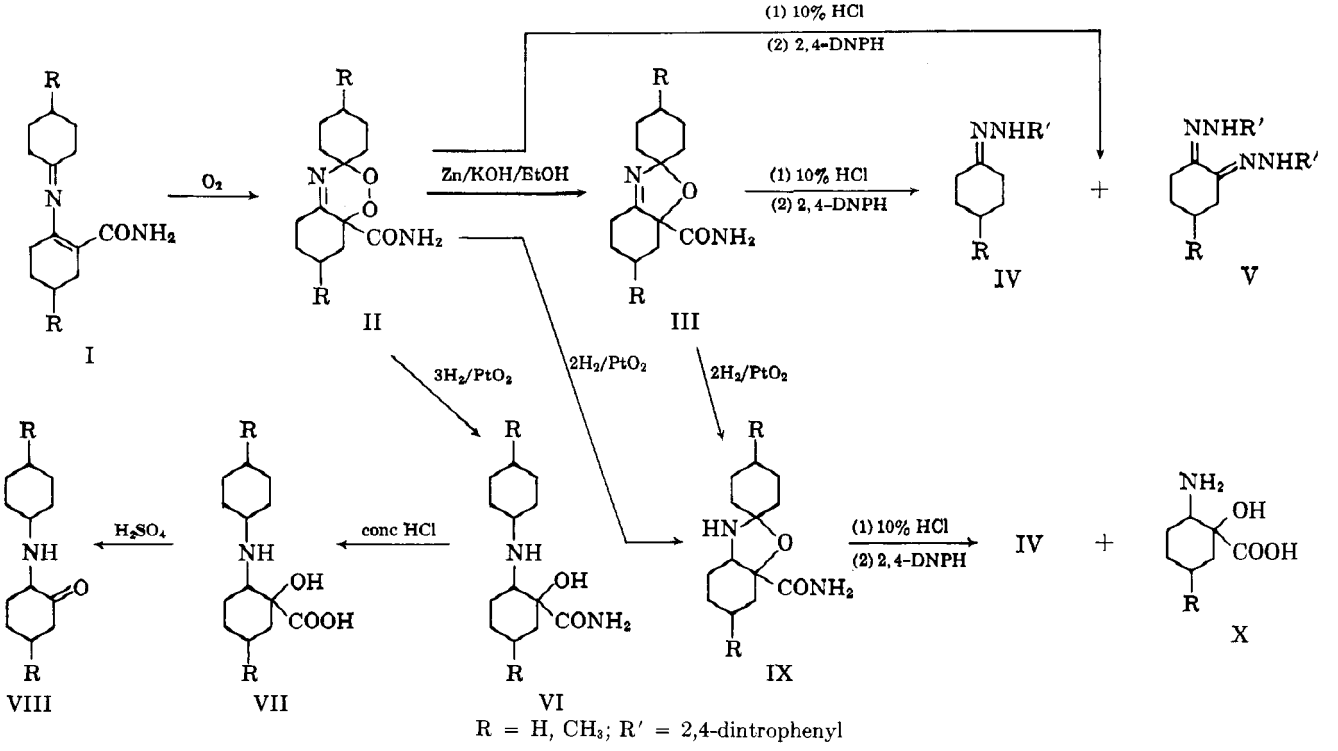
Cyclohexylidene-2-carbamylcyclohex-1-enylamine, 4-methylcyclohexylidene-2-carbamyl-4-methylcyclohex-1-enylamine, and 4-*t*-butylcyclohexylidene-2-carbamyl-4-*t*-butylcyclohex-1-enylamine readily absorb oxygen to form peroxides. The structures of these peroxides have been determined and some of their reactions are described.

Recently[1] the original structure assigned[2] to the condensation product from cyclohexanone and urea was confirmed and several compounds in this series were prepared[1] by condensing alicyclic ketones with urea. During the purification of these condensation products it was noted that they absorbed oxygen very readily. Cyclohexylidene-2-carbamylcyclohex-1-enylamine (I, R = H) in chloroform absorbed 1 mole equivalent of oxygen from an atmosphere of pure oxygen in approximately 50 min. In the presence of 0.1% of cobalt naphthenate, 1 mole equivalent of oxygen was absorbed in less than 5 min. The solid white peroxide (II, R = H) liberated iodine from iodide at room temperature. Titration of the free iodine can be used for the quantitative estimation of the peroxide.



R = H, CH_3; R' = 2,4-dintrophenyl

The peroxide (II, R = H) on complete hydrogenation in the presence of platinum oxide catalyst gave a monohydroxy derivative VI (R = H). Its n.m.r. spectrum[3] showed no peak normally associated with the C*H*OH group (6–6.5 p.p.m.). A sharp peak at 5.7 p.p.m. was attributed to the O*H* group and the hydroxy was assumed to be attached to a quaternary carbon atom. This was confirmed by hydrolysis of the amide (VI, R = H) to the corresponding acid (VII, R = H) and decarbonylation of the α-hydroxy acid by warming with concentrated sulfuric acid to give the ketone (VII, R = H).[4,5] Thus one oxygen of the peroxide is attached to the carbon carrying the carboxamide group. The other oxygen must be attached as shown in structure II because complete hydrolysis yielded 1,2-cyclohexanedione and cyclohexanone. If the second oxygen had been bonded to another carbon atom in the ring, hydrolysis would have given an amino-substituted cyclohexanol instead of cyclohexanone. This shows that the peroxide is formed by 1,4-addition of oxygen to the conjugated diene system of cyclohexylidene-2-carbamylcyclohex-1-enylamine. Farmer[6] had observed earlier that all examined peroxides of nonaromatic conjugated dienes were known to be produced by addition of oxygen at the terminals of the diene system. He gave several examples of peroxides formed by the 1,4-addition of oxygen to con-

(1) A. F. McKay, C. Podesva, E. J. Tarlton, and J.-M. Billy, *Can. J. Chem.*, in press.

(2) A. F. McKay, E. J. Tarlton, and C. Podesva, *J. Org. Chem.*, **26**, 76 (1961).

(3) N.m.r. spectrum was measured with Varian Model HR-60 spectrometer at 60 Mc.

(4) H. von Pechmann, *Ber.*, **17**, 2542 (1884).

(5) L. F. Fieser and M. Fieser, "Advanced Organic Chemistry," Reinhold Publishing Corp., New York, N. Y., 1961, p. 368.

(6) H. Farmer, *Trans. Faraday Soc.*, **42**, 228 (1945).

Table I

Infrared Absorption Band (cm.$^{-1}$) Assignments[a]

No.	R	Stretching modes: N—H[b]		C=N[b]	$CONH_2$[b]	Bending modes: N—H[b]
II	H	3210	3070	1695	1675	
II	CH_3	3220	3070	1690	1667	
II	$(CH_3)_3C$	3165	3045	1699	1673	
III	H	3200		1692	1662	
III	CH_3	3200	3060	1682	1665	
VI	H	3530 [OH]	3450 [OH]		1675	1566
VI	CH_3		3440 [OH]		1670	1566
VII·HCl	H	3327	3205	1733 [COOH]		1577
VIII·HCl	H	2505 [NH_3^+]	2400 [NH_3^+]	1730 [>C=O]		
X	H	3100				1615,[c] 1577,[c] 1525[c]
X	CH_3	3302	3135			1637,[c] 1584,[c] 1552[c]

[a] Infrared spectra were determined on Nujol mulls of the crystalline compounds. [b] Other group assignments noted in brackets. [c] Three bands characteristic of amino acid zwitterions and reflect NH_3^+ and COO^- vibrations.

jugated dienes. The position of the double bond in spiro[cyclohexane-1′,3-9-carbamyl-3(*H*)-5,6,7,8-tetrahydrobenzo-1,2,4-dioxazine] (II, R = H) was corroborated by its infrared spectrum (*cf.* Table I).

When spiro[cyclohexane-1′,3-9-carbamyl-3(*H*)-5,6,7,8-tetrahydrobenzo-1,2,4-dioxazine] (II, R = H) was reduced in an alkaline solution with zinc dust, one atom of oxygen was lost. The product was identified as spiro[cyclohexane-1′,2-8-carbamyl-2(*H*)-4,5,6,7-tetrahydrobenzo-1,3-oxazole] (III, R = H). Compound III (R = H) on hydrolysis gave cyclohexanone and 1,2-cyclohexanedione which confirmed the positions of the oxygen linkages. The position of the double bond was noted from its infrared spectrum. This double bond was reduced in the presence of platinum oxide in acid solution. The product, spiro[cyclohexane-1′,2-8-carbamyl-2(*H*)-3,9,4,5,6,7-hexahydrobenzo-1,3-oxazole] (IX, R = H) on hydrolysis gave cyclohexanone and 2-amino-1-hydroxycyclohexanecarboxylic acid (X). The amino acid (X, R = H) was identified by analysis and infrared spectrum (*cf.* Table I).

The reactions described before for cyclohexylidene-2-carbamylcyclohex-1-enylamine (I, R = H) were repeated with 4-methylcyclohexylidene-2-carbamyl-4-methylcyclohex-1-enylamine (I, R = CH_3). Spiro[4′-*t*-butylcyclohexane-1′,3-7-*t*-butyl-9-carbamyl-3(*H*)-5,6,7,8-tetrahydrobenzo-1,2,4-dioxazine] (II, R = $(CH_3)_3C$-) also was prepared during these studies.

Experimental[7]

Spiro[cyclohexane-1′,3-9-carbamyl-3(*H*)-5,6,7,8-tetrahydrobenzo-1,2,4-dioxazine] (II, R = H).—A solution of cyclohexylidene-2-carbamylcyclohex-1-enylamine (22.7 g., 0.1 mole) in chloroform (750 ml.) in hydrogenation equipment was stirred under an atmosphere of pure oxygen at ambient temperature and pressure. One mole equivalent of oxygen was absorbed in 60 min. and the peroxide began to separate from solution within 15 min. The product (m.p. 194° dec.) was recovered by filtration; yield, 22.6 g. (87%). Recrystallization from ethanol (100 ml./g.) did not raise the melting point.

Anal. Calcd. for $C_{13}H_{20}N_2O_3$: C, 61.89; H, 7.99; N, 11.11. Found: C, 62.11; H, 7.86; N, 10.94.

Spiro[4′-methylcyclohexane-1′,3-7-methyl-9-carbamyl-3(*H*)-5,6,7,8-tetrahydrobenzo-1,2,4-dioxazine] (II, R = CH_3).—This compound (m.p. 192° dec.) was prepared in 73% yield by the preceding method. One recrystallization from ethanol (100 ml./g.) raised the melting point to 199° dec.

Anal. Calcd. for $C_{15}H_{24}N_2O_3$: C, 64.30; H, 8.63; N, 9.98. Found: C, 64.37; H, 8.64; N, 10.01.

(7) All melting points are uncorrected. Microanalyses were performed by Dr. C. Daessle, Montreal, Quebec.

A sample (96.3 mg.) of this peroxide in glacial acetic acid (20 ml.) and water (10 ml.) containing sodium iodide (0.5 g.) was allowed to stand for 10 min. Titration of the liberated iodine with 0.0515 *N* sodium thiosulfate gave an equivalent weight for the peroxide of 282 (calcd. equiv. wt., 280.36).

Spiro[4′-*t*-butylcyclohexane-1′,3-7-*t*-butyl-9-carbamyl-3(*H*)-5,6,7,8-tetrahydrobenzo-1,2,4-dioxazine] (II, R = $(CH_3)_3C$).—This peroxide (m.p. 215–220° dec.) was prepared in quantitative yield by the method described earlier for the preparation of spiro[cyclohexane-1′,3-9-carbamyl-3(*H*)-5,6,7,8-tetrahydrobenzo-1,2,4-dioxazine]. One crystallization from ethanol raised the melting point to 218–220° dec.

Anal. Calcd. for $C_{21}H_{36}N_2O_3$: C, 69.20; H, 9.95; N, 7.68. Found: C, 68.95; H, 9.76; N, 7.63.

Hydrolysis of Spiro[cyclohexane-1′,3-9-carbamyl-3(*H*)-5,6,7,8-tetrahydrobenzo-1,2,4-dioxazine] (II, R = H).—A suspension of this dioxazine (1 g., 0.004 mole) in 10% aqueous hydrochloric acid was heated under reflux for 70 min. After the cooled solution was diluted with an equal volume of water, it was extracted with two 25-ml. portions of pentane. One-half the combined pentane extracts was taken to dryness and the residue was converted into a 2,4-dinitrophenylhydrazone (m.p. 157–158°); yield, 0.28 g. (50%). Crystallization from ethyl acetate raised the melting point to 159–160°. This melting point was not depressed on admixture with a known sample of cyclohexanone 2,4-dinitrophenylhydrazone (m.p. 159–160°).

One-half of the aqueous phase was heated under reflux for 15 min. with 2,4-dinitrophenylhydrazine (1.2 g. in 48 ml. of methanol containing 4% concentrated hydrochloric acid). On cooling adipoin 2,4-dinitrophenylosazone (m.p. 210° dec.) deposited as deep red crystals; yield, 0.26 g. (28%). One recrystallization from ethyl acetate raised the melting point to 232° dec. A mixture melting point determination with a known sample of adipoin 2,4-dinitrophenylosazone (m.p. 232–233° dec.) gave no depression.

Anal. Calcd. for $C_{18}H_{18}N_8O_8$: C, 45.80; H, 3.39; N, 23.70. Found: C, 45.88; H, 3.39; N, 23.60.

Hydrolysis of Spiro[4′-methylcyclohexane-1′,3-7-methyl-9-carbamyl-3(*H*)-5,6,7,8-tetrahydrobenzo-1,2,4-dioxazine] (II, R = CH_3).—Two grams (0.007 mole) of this peroxide was hydrolyzed and the solution treated under the conditions described before for the hydrolysis of spiro[cyclohexane-1′,3-9-carbamyl-3(*H*)-5,6,7,8-tetrahydrobenzo-1,2,4-dioxazine]. The pentane extract gave the 2,4-dinitrophenylhydrazone (m.p. 127–130°) of 4-methylcyclohexanone in 44% yield. One recrystallization from ethyl acetate raised the melting point to 131–132°. A mixture melting point determination with a known sample of 4-methylcyclohexanone 2,4-dinitrophenylhydrazone (m.p. 131–132°) was not depressed.

The aqueous layer on treatment with 2,4-dinitrophenylhydrazine gave the di-2,4-dinitrophenylhydrazone (m.p. 187° dec.) of 4-methylcyclohexane-1,2-dione in 28% yield. Recrystallization from ethyl acetate raised the melting point to 199° dec.

Anal. Calcd. for $C_{19}H_{18}N_8O_8$: C, 46.91; H, 3.73; N, 23.03. Found: C, 47.19; H, 4.01; N, 23.31.

Spiro[cyclohexane-1′,2-8-carbamyl-2(*H*)-4,5,6,7-tetrahydrobenzo-1,3-oxazole] (III, R = H).—Spiro[cyclohexane-1′,3-9-carbamyl-3(*H*)-5,6,7,8-tetrahydrobenzo-1,2,4-dioxazine] (5 g., 0.02 mole) was added to a suspension of zinc dust (25 g.) in ethano-

lic potassium hydroxide (25 g. of potassium hydroxide in 500 ml. of ethanol) and the mixture was heated under reflux for 30 min. After the hot reaction mixture was filtered, the filtrate was evaporated to dryness *in vacuo*. The residue was dissolved in water and the aqueous solution was extracted with chloroform. Evaporation of the chloroform gave 4.9 g. of amber solid. Crystallization from ethyl acetate gave white needles (m.p. 136–137°); yield, 3.7 g. (79%). One recrystallization from ethyl acetate raised the melting point to 139–140°.

Anal. Calcd. for $C_{13}H_{20}N_2O_2$: C, 66.07; H, 8.53; N, 11.86. Found: C, 65.90; H, 8.53; N, 12.05.

Spiro[4′-methylcyclohexane-1′,2-6-methyl-8-carbamyl-2(*H*)-4,5,6,7-tetrahydrobenzo-1,3-oxazole] (III, R = CH_3).—Spiro-[4′-methylcyclohexane-1′,2-6-methyl-8-carbamyl-2(*H*)-4,5,6,7-tetrahydrobenzo-1,3-oxazole] was prepared from spiro[4′-methylcyclohexane-1′,3-7-methyl-9-carbamyl-5,6,7,8-tetrahydrobenzo-1,2,4-dioxazine] by the method described before for the preparation of spiro[cyclohexane-1′,2-8-carbamyl-2(*H*)-4,5,6,7-tetrahydrobenzo-1,3-oxazole]. The residue from the chloroform extract crystallized from ether in large cubes (m.p. 170–178°); yield, 1.3, g. (67%). One recrystallization from ether raised the melting point to 180–181°.

Anal. Calcd. for $C_{15}H_{24}N_2O_2$: C, 68.14; H, 9.15; N, 10.60. Found: C, 68.12; H, 9.16; N, 10.48.

Hydrolysis of Spiro[cyclohexane-1′,2-8-carbamyl-2(*H*)-4,5,6,7-tetrahydrobenzo-1,3-oxazole] (III, R = H).—Hydrolysis of spiro[cyclohexane-1′,2-8-carbamyl-2(*H*)-4,5,6,7-tetrahydrobenzo-1,3-oxazole] under the conditions described earlier for the hydrolysis of spiro[cyclohexane-1′,3-9-carbamyl-3(*H*)-5,6,7,8-tetrahydrobenzo-1,2,4-dioxazine] gave a 49% yield of cyclohexanone 2,4-dinitrophenylhydrazone (159°) and a 72% yield of adipoin 2,4-dinitrophenylosazone (m.p. 232° dec.). The products were identified by mixture melting point determinations.

Cyclohexyl-2-hydroxy-2-carbamylcyclohexylamine (VI, R = H).—Spiro[cyclohexane-1′,3-9-carbamyl-3(*H*)-5,6,7,8-tetrahydrobenzo-1,2,4-dioxazine] (2 g., 0.008 mole) in absolute ethanol (250 ml.) containing concentrated hydrochloric acid (0.66 ml., 0.008 mole) and platinum oxide (200 mg.) was hydrogenated at ambient temperature and pressure. Three mole equivalents of hydrogen (597 ml.) were absorbed in 20 min. After the catalyst was removed by filtration, the filtrate was evaporated to dryness *in vacuo*. The residue was crystallized from ethanol–ether solution, yield 1.6 g. (67%). The melting point of the hydrochloride salt was raised from 247° to 250–251° by a second crystallization from the same solvent.

Anal. Calcd. for $C_{13}H_{24}N_2O_2 \cdot HCl \cdot {}^1/_2C_2H_5OH$: C, 56.08; H, 9.41; Cl, 11.83; N, 9.34. Found: C, 55.95; H, 9.37; Cl, 12.07; N, 9.33.

The solvent of crystallization was not removed from this salt by prolonged heating at 100° *in vacuo*.

A sample of cyclohexyl-2-hydroxy-2-carbamylcyclohexylamine hydrochloride (4 g.) was dissolved in water and the solution was made alkaline with 8% aqueous sodium hydroxide. The oil was removed by extraction with ether. Concentration of the ether extract gave crystals melting at 143–144°; yield, 2.8 g. (87%). One recrystallization from ether raised the melting point to 145°.

Anal. Calcd. for $C_{13}H_{24}N_2O_2$: C, 64.97; H, 10.06; N, 11.66. Found: C, 65.21; H, 10.18; N, 11.67.

4-Methylcyclohexyl-2-hydroxy-2-carbamyl-4-methylcyclohexylamine (VI, R = CH_3).—Hydrogenation of spiro[4′-methylcyclohexane-1′,3-7-methyl-9-carbamyl-3(*H*)-5,6,7,8-tetrahydrobenzo-1,2,4-dioxazine] under the conditions described earlier for the preparation of cyclohexyl-2-hydroxy-2-carbamylcyclohexylamine gave a 94% yield of 4-methylcyclohexyl-2-hydroxy-2-carbamyl-4-methylcyclohexylamine hydrochloride (m.p. 264–265° dec.). Several crystallizations from ethanol–ether solution raised the melting point to 279° dec.

Anal. Calcd. for $C_{15}H_{29}ClN_2O_2$: C, 59.09; H, 9.59; Cl, 11.63; N, 9.17. Found: C, 59.06; H, 9.62; Cl, 11.81; N, 9.12.

An aqueous solution of this hydrochloride (2.7 g., 0.009 mole) was made alkaline with aqueous sodium bicarbonate. An oil separated which was recovered by extraction with ether. Concentration of the ether solution gave crystals (m.p. 107–114°) of 4-methylcyclohexyl-2-hydroxy-2-carbamyl-4-methylcyclohexylamine; yield, 1.7 g. (71%). One recrystallization from ether raised the melting point to 114–115°.

Anal. Calcd. for $C_{15}H_{28}N_2O_2$: C, 67.11; H, 10.52; N, 10.44. Found: C, 67.11; H, 10.54; N, 10.46.

Cyclohexyl-2-hydroxy-2-carboxycyclohexylamine Hydrochloride (VII, R = H).—Cyclohexyl-2-hydroxy-2-carbamylcyclohexylamine hydrochloride (1 g., 0.003 mole) in concentrated hydrochloric acid (25 ml.) was heated on a steam bath for 2 hr. After evaporation of the solution to a small volume, crystals (m.p. 254–257° dec.) separated; yield, 0.8 g. (88%). One recrystallization from methanol–ether solution raised the melting point to 260–261° dec.

Anal. Calcd. for $C_{13}H_{24}ClNO_3$: C, 56.21; H, 8.71; Cl, 12.76; N, 5.04. Found: C, 56.27; H, 8.82; Cl, 12.95; N, 5.20.

Cyclohexyl-2-oxocyclohexylamine (VIII, R = H).—Cyclohexyl-2-hydroxy-2-carboxycyclohexylamine hydrochloride (1 g., 0.003 mole) was dissolved in concentrated sulfuric acid (7.5 g.). After the evolution of hydrogen chloride had subsided, the solution was heated at 80–90° for 30 min. or until carbon monoxide evolution ceased. The solution was cooled, diluted with water, and made alkaline with 10% aqueous sodium hydroxide. Colorless liquid cyclohexyl-2-oxocyclohexylamine separated from the alkaline solution; yield, 0.6 g. (85%). This liquid was unstable and it rapidly turned green.

A sample of freshly prepared cyclohexyl-2-oxocyclohexylamine (0.6 g., 0.003 mole) was treated with a solution of 2,4-dinitrophenylhydrazine (0.6 g., 0.003 mole) in methanol (30 ml.) containing 4% concentrated hydrochloric acid. The 2,4-dinitrophenylhydrazone of cyclohexyl-2-oxocyclohexylamine hydrochloride separated out in 59% yield. The melting point of 221–222° dec. was not changed by recrystallization.

Anal. Calcd. for $C_{18}H_{26}ClN_5O_4$: C, 52.49; H, 6.36; Cl, 8.61; N, 17.00. Found: C, 52.54; H, 6.50; Cl, 8.55; N, 16.84.

Dry hydrogen chloride was bubbled through an absolute ether solution (25 ml.) of cyclohexyl-2-oxocyclohexylamine (0.5 g., 0.002 mole). The hydrochloride salt precipitated immediately; yield, 0.56 g. (94%). Crystallization from ethanol–ether raised the melting point from 224–230° to 243–243.5° dec.

Anal. Calcd. for $C_{12}H_{22}ClNO$: C, 62.19; H, 9.57; Cl, 15.30; N, 6.04. Found: C, 62.43; H, 9.34; Cl, 15.57; N, 6.03.

Spiro[cyclohexane-1′,2-8-carbamyl-2(*H*)-3,9,4,5,6,7-hexahydrobenzo-1,3-oxazole] (IX, R = H). Method A.—A solution of spiro[cyclohexane-1′,2-8-carbamyl-2(*H*)-4,5,6,7-tetrahydrobenzo-1,3-oxazole] (1 g., 0.004 mole) in absolute ethanol (30 ml.) containing platinum oxide (40 mg.) was hydrogenated at ambient temperature and pressure. One mole equivalent of hydrogen was absorbed in 2.5 hr. After the catalyst was removed, the filtrate on concentration gave 0.76 g. (75%) of crude product (m.p. 157–172°). The melting point was raised to a constant value of 185–186° by crystallization from ethyl acetate.

Anal. Calcd. for $C_{13}H_{22}N_2O_2$: C, 65.51; H, 9.31; N, 11.75. Found: C, 65.40; H, 9.54; N, 11.71.

Method B.—Spiro[cyclohexane-1′,3-9-carbamyl-3(*H*)-5,6,7,8-tetrahydrobenzo-1,2,4-dioxazine] (3 g., 0.012 mole) in absolute ethanol (300 ml.) containing platinum oxide (200 mg.) was hydrogenated at room temperature and pressure. Two mole equivalents of hydrogen were absorbed in 1 hr. after which the catalyst was removed by filtration. The residue from evaporation of the filtrate was crystallized from ethyl acetate; yield, 2.3 g. (82%). Three recrystallizations from ethyl acetate raised the melting point from 158–178° to 184–185°; yield, 1.2 g. This product did not depress the melting point of a sample of spiro[cyclohexane-1′,2-8-carbamyl-2[*H*]-3,9,4,5,6,7-hexahydrobenzo-1,3-oxazole] (m.p. 185–186°) prepared by method A.

Spiro[4′-methylcyclohexane-1′,2-6-methyl-8-carbamyl-2(*H*)-3,9,4,5,6,7-hexahydrobenzo-1,3-oxazole] (IX, R = CH_3).—Hydrogenation of spiro[4′-methylcyclohexane-1′,2-6-methyl-8-carbamyl-2(*H*)-4,5,6,7-tetrahydrobenzo-1,3-oxazole] under the conditions described above in method A for the hydrogenation of spiro[cyclohexane-1′,2-8-carbamyl-2(*H*)-4,5,6,7-tetrahydrobenzo-1,3-oxazole] gave a 30% yield of spiro[4′-methylcyclohexane-1′,-2-6-methyl-8-carbamyl-2(*H*)-3,9,4,5,6,7-hexahydrobenzo-1,3-oxazole] (m.p. 196–198°). One recrystallization from methanol–ether solution raised the melting point to 197–198°.

Anal. Calcd. for $C_{15}H_{26}N_2O_2$: C, 67.62; H, 9.84; N, 10.52. Found: C, 67.48; H, 9.81; N, 10.36.

Hydrolysis of Spiro[cyclohexane-1′,2-8-carbamyl-2(*H*)-3,9,-4,5,6,7-hexahydrobenzo-1,3-oxazole].—A solution of this oxazole (0.4 g., 0.0017 mole) in 10% aqueous hydrochloric acid (20 ml.) was heated on a steam bath for 90 min. After the solution was cooled to room temperature, it was extracted with two 20-ml. portions of pentane. The aqueous phase was taken to dryness and the residue (0.37 g.) in 50% aqueous ethanol was added to a column of Dowex 50-WX2 resin (20 ml.) in acid form. The

column was washed with aqueous ethanol until the eluate was free from chloride ion. After this the column was washed with 5% aqueous ammonium hydroxide solution and the ammoniacal eluate evaporated. The crude 2-amino-1-hydroxycyclohexanecarboxylic acid melted at 287–288° dec.; yield, 0.2 g. (78%). One crystallization from methanol raised the melting point to a constant value of 294–295° dec.; yield, 0.16 g.

Anal. Calcd. for $C_7H_{13}NO_3$: C, 52.81; H, 8.23; N, 8.81. Found: C, 53.01; H, 8.03; N, 8.78.

The residue from the pentane extract on treatment with 2,4-dinitrophenylhydrazine in methanol–hydrochloric acid under the conditions previously described gave a 77% yield of cyclohexanone 2,4-dinitrophenylhydrazone (m.p. 159–160°). This product was identified by a mixture melting point determination.

Hydrolysis of Spiro[4′-methylcyclohexane-1′,2-6-methyl-8-carbamyl-2(*H*)-3,9,4,5,6,7-hexahydrobenzo-1,3-oxazole].—Spiro[4′-methylcyclohexane-1,2-6-methyl-8-carbamyl-4,5,6,7-tetrahydrobenzo-1,3-oxazole] was hydrolyzed under the conditions described earlier for the hydrolysis of spiro[cyclohexane-1′,2-8-carbamyl-2(*H*)-3,9,4,5,6,7-hexahydrobenzo-1,3-oxazole]. The pentane extract residue on treatment with 2,4-dinitrophenylhydrazine reagent gave a 57% yield of 4-methylcyclohexanone 2,4-dinitrophenylhydrazone (m.p. 132–133°). This product was identified by a mixture melting point determination.

The acidic aqueous solution from the pentane extract was evaporated to dryness and the residue in aqueous ethanol was added to a Dowex 50-WX2 resin. 2-Amino-1-hydroxy-5-methylcyclohexanecarboxylic acid (m.p. 279–280° dec.) was isolated in 56% yield in the same manner described before for the isolation of 2-amino-1-hydroxycyclohexanecarboxylic acid. One recrystallization from methanol–ether solution raised the melting point to 288–289° dec.

Anal. Calcd. for $C_8H_{15}NO_3$: C, 55.48; H, 8.73; N, 8.09. Found: C, 55.66; H, 8.76; N, 8.14.

Solvent Effects. The Solvolysis Rates of Cyclopropylcarbinyl, 1-Methylcyclopropylcarbinyl, and 1-Phenylcyclopropylcarbinyl Arenesulfonate Derivatives

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The benzene-, *p*-methoxybenzene-, and *p*-toluenesulfonate derivatives of cyclopropylcarbinol (Ia–c), 1-methylcyclopropylcarbinol (IIa–c), and 1-phenylcyclopropylcarbinol (IIIa–c) have been solvolyzed in acetic acid at various temperatures. The relative first-order rates of acetolysis at 20° were found to be $k_{Ib} = 1$, $k_{IIb} = 4$, and $k_{IIIb} = 1.6$. The activation energy parameters for Ia–c differed greatly from those for IIa–c or IIIa–c and similarly Ib exhibited a different sensitivity to solvent ionizing strength. The β-substituent effects, differences in activation energy parameters, sensitivities to solvent ionizing strength, and solvolysis products of these arenesulfonates are discussed in terms of solvated transition state differences.

The observation that a phenyl substituent at the 1-ring position in cyclopropylcarbinyl benzenesulfonate produced no significant rate acceleration in an acetolysis reaction[1] led to a more detailed study of this phenomenon. It was of particular interest to determine the activation energy parameters for the acetolysis of cyclopropylcarbinyl arenesulfonate compounds. Such information would assist in a mechanistic diagnosis of the apparent lack of a substituent effect. In addition, the sensitivity of the solvolytic reactions of both cyclopropylcarbinyl and 1-phenylcyclopropylcarbinyl arenesulfonate derivatives to solvent ionizing strength and arenesulfonate leaving group were determined.

The kinetic data are summarized in Table I. Each of these esters was allowed to solvolyze in the indicated solvent and the course of reaction followed by titrating the liberated arenesulfonic acid. The acetolysis reactions of the cyclopropylcarbinyl arenesulfonates demonstrated the previously reported "internal return" rearrangement[2] which accounted for about one-third of the starting material. The solvolysis rates, consequently, of Ia–c were calculated from the initial slope of the rate curves.[3] All other reactions were strictly first order in arenesulfonate and furnished, within experimental error, 100% of the theoretical amount of acid present.

Table II compares the relative rates of acetolysis of three cyclopropylcarbinyl 1-methyl- and 1-phenylcyclopropylcarbinyl arenesulfonates at 20° with the relative rates of acetolysis of correspondingly substituted acyclic *p*-toluenesulfonates at 75°. It can be seen that, in the acetolysis of the cyclopropylcarbinyl esters, the rate-enhancing abilities of the methyl and phenyl groups are in distinct contrast to their effectiveness in the acetolysis of the acyclic analogs. This apparent lack of β-substituent effect is further emphasized by the fact that 1-methylcyclopropylcarbinyl chloride suffers solvolysis in 50 vol. % aqueous ethanol at 50°, some fifty times faster than cyclopropylcarbinyl chloride.[6]

Although the free energy of activation is similar for Ia–c, IIa–c, and IIIa–c, the partitioning of the thermodynamic functions of activation is markedly different for Ia–c in respect to IIa–c or IIIa–c. That the functions under discussion represent real differences and not random error is shown by the constancy of the data with the three different leaving groups.[7] While

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(6) E. F. Cox, M. C. Caserio, M. S. Silver, and J. D. Roberts, *ibid.*, **83**, 2719 (1961).

(7) The activation energy parameters for IIIa and IIIb previously were reported[1] on the basis of a three-point regression analysis over 12° and 15° temperature ranges, respectively. Fivefold replication of this work in the present study over 17° and 20° temperature ranges, respectively, revealed that the reported rate constant[1] for the acetolysis of IIIa at 18° was sufficiently displaced from the calculated regression line (20% low) to produce an erroneously high slope value. Also, the reported rate constant[1] for IIIb at 25° was sufficiently displaced from the calculated regression line (28% low) to produce an erroneously low slope value. Due to the few points over a limited temperature range, this error did not show up as significant in the regression analysis. Correlation coefficients of 0.999 were obtained in the present study for both IIIa and IIIb. The *t*-test gave $t = -134.3$, with 42 degrees of freedom, $P < .005$ for IIIa and $t = -239.0$, with 41 degrees of freedom, $P < .005$ for IIIb.