BULLETIN OF THE CHEMICAL SOCIETY OF JAPAN, VOL. 45, 636—638 (1972)

Studies on Stable Free Radicals. VIII.[1] The Synthesis and Oxidation of Hindered 4-Oxopiperidine Derivatives

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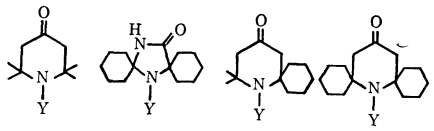
(Received July 22, 1971)

It has been reported that a hindered amine, 2,2,6,6-tetramethyl-4-oxopiperidine (I), was easily oxidized with 30% aqueous hydrogen peroxide in the presence of EDTA and sodium tungstate to give a free radical, 2,2,6,6-tetramethyl-4-oxopiperidine-1-oxyl (II), which was extremely stable in air at room temperature.[2] However, cyclohexane-1-spiro-2′-(4′-oxoimidazolidine)-5′-spiro-1″-cyclohexane (III)[3] did not give the corresponding *N*-oxyl IV (Chart I) and was quantitatively recovered under similar reaction conditions. The difference in the reactivities of I and III can be explained *a priori* by the following factors: a) the effect of the alkyl groups at *C*-2 and *C*-6 (or *C*-5 in imidazolidine ring), b) the character of a heterocyclic ring system. In order to establish the contribution of a), the monocyclohexane derivative V and the dicyclohexane derivative VI (Chart I)



I Y=H III Y=H V Y=H VI Y=H
II Y=O· IV Y=O· VII Y=O· VIII Y=O·

Chart I

were synthesized as is shown in Chart II; the relative ease of the oxidation of V and VI with 30% aqueous hydrogen peroxide into the corresponding *N*-oxyls VII and VIII respectively, was then qualitatively compared with that of I into II.[4] Utilizing a slight modification (in methanol) of the method of Rozantzev,[3] the oxidation of I and V with 30% aqueous hydrogen peroxide into II and VII respectively in good yields was successful, although the ease of the formation of the *N*-oxyl VII was observed to be slightly smaller than that of II. On the other hand, the oxidation of VI into VIII was unsuccessful under the same reaction conditions, and we recovered the starting amine VI. Thus, it was supposed that one of the major factors[4] influencing the rate of the oxidation of such amines is a steric effect. The synthesis of VIII in a good yield was achieved by the oxidation of VI with *m*-chloroperbenzoic acid(CPBA).

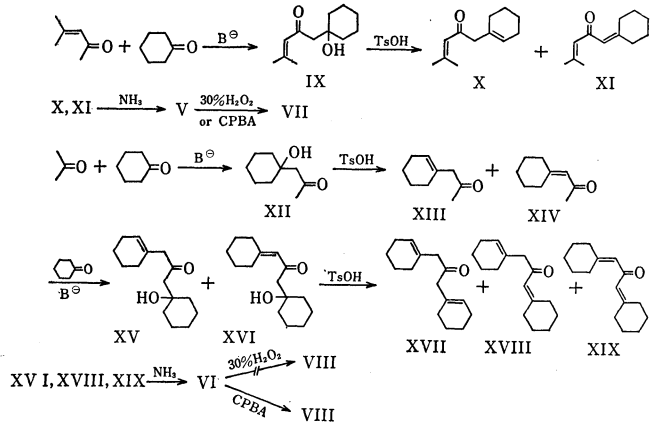


Chart II

Experimental

All the melting points are uncorrected.

Unless otherwise stated, the IR spectra were taken with a Hitachi EPI-S2 spectrometer (Nujol mull or liquid film); the NMR spectra, with a Varian A-60 apparatus, using tetramethylsilane as the internal reference; the mass spectra, with a JEOL-JMS-OIS apparatus, and the ESR spectra, with a Hitachi MES 4001-type X-band apparatus, employing 100-kHz modulation. Table 1 shows the formulae, molecular ion peaks, melting points, boiling points, yields and results of the elemental analysis of all the products, while the spectral data are shown in Table 2.

1-(1-Hydroxycyclohexyl)-4-methylpent-3-en-2-one (*IX*). Into a suspension of 1.00 mol of sodium ethoxide in 500 m*l* of toluene[5] was added slowly and dropwise a mixture of 100 g (1.02 mol) of cyclohexanone and 100.2 g (1.04 mol) of mesityl oxide at −55°C under nitrogen with stirring. After additional stirring for 30 min at −50°C, the reaction mixture was poured into a mixture of 101 g of 35% hydrochloric acid and 700 g of crashed ice. The resulting mixture was allowed to stand at 0°C for 1 hr and then at room temperature overnight. The organic layer was separated, and the aqueous phase was extracted with ether. The combined organic phases were washed three times with water saturated with sodium chloride, and then dried over anhydrous magnesium sulfate. The removal of the solvents and fractional distillation gave 150.3 g of IX.

1-(1-Hydroxycyclohexyl)propan-2-one (*XII*) was similarly prepared from acetone and cyclohexanone.

1-(Cyclohex-1-enyl)-3-(1-hydroxycyclohexyl)propan-2-one (*XV*) *Containing 1-(Cyclohexylidene)-3-(1-hydroxycyclohexyl)propan-2-one* (*XVI*). Similarly, a *ca.* 9 : 1 mixture of XV and XVI was prepared from cyclohexanone and the ketone, XIII, containing XIV.

General Procedure for Dehydration of Ketols IX, XII, XV, and

1) Part VII: T. Toda, S. Morimura, and K. Murayama, This Bulletin, **45**, 557 (1972).

2) a) E. G. Rozantzev, "Free Nitroxyl Radicals," Plenum Press, New York, N. Y. (1970), p. 1. b) K. Murayama, *Yuki Gosei Kagaku Kyokaishi*, **29**, 366 (1971).

3) K. Murayama, S. Morimura, and T. Yoshioka, This Bulletin, **42**, 1640 (1969).

4) Following papers will describe with respect to hindered imidazolidines and piperazines.

5) R. B. Turner and D. M. Voitle, *J. Amer. Chem. Soc.*, **72**, 4166 (1950).

Table 1.

Compound	Formula	M+ (*m/e*)	Mp °C(Solvent for recry.) Bp °C/mmHg	Yield (%)	Elemental analysis (Found/Calcd)		
					C	H	N
V	$C_{12}H_{21}NO \cdot H_2O$	195	50.5—51.5 (acetone: H_2O=2 : 1) 84—87/0.5 (anhydrous oil)	76.8	67.40/67.60	10.82/10.89	6.61/6.57
VI	$C_{15}H_{25}NO$	235	100.5—101.5 (acetone)	89.5	76.53/76.60	10.72/10.72	6.17/5.95
VII	$C_{12}H_{20}NO_2$	210	83.0—84.0 (*n*-hexane)	83.8	68.38/68.53	9.65/ 9.59	6.72/6.66
VIII	$C_{15}H_{24}NO_2$	250	114.0—115.0 (petroleum ether containing benzene)	62.0	71.86/71.96	9.66/ 9.66	5.52/5.59
IX	$C_{12}H_{20}O_2$		105/1.5	75.5	73.24/73.47	10.29/10.20	
X	$C_{12}H_{18}O$[a]		80—81/1	80	80.61/80.85	10.19/10.18	
XII	$C_9H_{16}O_2$	156	67—68/1	32.6	69.31/69.23	10.36/10.38	
XIII	$C_9H_{14}O$[b]	138	82—83/13	75.5	78.03/78.26	10.25/10.22	
XV	$C_{15}H_{24}O_2$[c]	236	128—132/2	30	76.34/76.22	10.10/10.24	
XVII	$C_{15}H_{22}O$[d]	218	124—125/1.5	65	82.85/82.57	10.20/10.18	

a): containing XI, b): containing XIV, c): containing XVI, d): containing XVIII and XIX

Table 2. Spectral data

Compound	IR (cm^{-1})	NMR (τ)
V[a]	3480, 3340(w), 3250, 1715(sh), 1690[b]	7.71(4H, s), 8.76(6H, s), 8.3—8.8(10H, broad)[c]
VI	3280, 1700(sh), 1690[b]	7.67(4H, s), 8.2—9.0(20H, broad)[c]
VII	1710, 1322, 1234[b]	
VIII	1725, 1324, 1212[b]	
IX	3500, 1680, 1620	4.05(1H, m, J=1.2 Hz), 6.55(1H, broad), 7.58[d](2H, s), 7.90(3H, d, J=1.2 Hz), 8—9(10H, broad)
X	1715(sh), 1690, 1670(sh), 1625[e]	3.9(1H, m, J=1.5 Hz), 4.3—4.6(1H, broad m)[d,f], 7.0—7.2(2H, broad m), 7.90(3H, d, J=1.5 Hz), 8.13(3H, d, J=1.5 Hz), 7.8—8.6(broad)
XI[e]		3.9(1H, m, J=1.5 Hz), 4.1(1H, broad m), 7.90[d,f](3H, d, J=1.5 Hz), 8.13(3H, d, J=1.5 Hz), 7.8—8.9(broad)
XII	3490, 1700[b]	6.78(1H, broad), 7.50(2H, s), 7.87(3H, s), 7.87(3H, s), 8—9[d](10H, broad)
XIII	1720, 1690(w), 1670(sh), 1625[g]	4.45(1H, m), 7.06(2H, broad m), 7.93(3H, s)[d,f], 7.8—8.7 (broad)
XIV[g]		4.06(1H, m), 7.90(3H, s), 7.8—8.7(broad)[d,f]
XV	3500, 1700, 1670(sh), 1615[h]	4.3—4.5(1H, m), 6.1—6.5(1H, broad), 6.9—7.1[d,f](2H, broad m), 7.41(2H, s), 7.7—9.0(broad)
XVI[h]		4.0—4.1(1H, m), 6.1—6.5(1H, broad), 7.41(2H[d,f], s), 7.7-9.0(broad)
XVII	1720, 1690, 1670, 1625[i]	4.5(2H, m), 6.9—7.3(4H, broad m), 7.7—8.7[d,f](broad)
XVIII[i]		4.1(1H, m), 4.5(1H, m), 6.9—7.3(2H, broad m)[d,f], 7.7—8.7(broad)
XIX[i]		4.1(2H, m), 7.7—8.7(broad)[d,f]

a) as monohydrate, b) PE-221, c) in $CDCl_3$, d) in CCl_4, e) a mixture of X and XI, f) X/XI=*ca.* 75/25, XIII/XIV=*ca.* 85/15, XV/XVI=*ca.* 90/10, XVII/XVIII/XIX=*ca.* 63/34/3 on the basis of NMR, g) a mixture of XIII and XIV, h) a mixture of XV and XVI, i) a mixture of XVII, XVIII and XIX

XVI, A solution of ketols in benzene was refluxed for 1.5 hr in the presence of *p*-toluenesulfonic acid, using a Dean-Stark separator. After cooling the reaction mixture was washed with water and dried over anhydrous magnesium sulfate. After the removal of the solvent and fractional distillation, IX gave a *ca.* 3 : 1 mixture of *1-(cyclohex-1-enyl)-4-methylpent-3-en-2-one* (*X*) and *1-cyclohexylidene-4-methylpent-3-en-2-one* (*XI*), identified on the basis of the signal intenisty in the NMR spectrum. Similarly, XII gave a *ca.* 85 : 15 mixture of *1-(cyclohex-1-enyl)propan-2-one* (*XIII*) and *1-cyclohexylidenepropan-2-one* (*XIV*) (NMR). Without the separation of XV and XVI, these were dehydrated to give a *ca.* 63 : 34 : 3 mixture of *1,3-(dicyclohex-1-enyl)propan-2-one* (*XVII*), *1-(cyclohex-1-enyl)-3-cyclohexylidenepropan-2-one* (*XVIII*) and *1,3-dicyclohexylidenepropan-2-one* (*XIX*) (NMR).

1-Aza-2,2-dimethyl-4-oxo-spiro[5.5]undecane (*V*). Without the separation of X and XI, these substances(8.7 g, 49.8 mmol) were treated with 12.4 g(730 mmol) of ammonia in 8.7 m*l* of water and 35 m*l* of methanol at 105—110°C for 17 hr in a pressure bottle (glass).[6,7] After the removal of the ammonia and the solvents, the reaction mixture was dissolved into petroleum ether and treated with active char-

6) D. Mackay and W. A. Waters, *J. Chem. Soc., C*, **1966**, 814.

7) It was inferable that the amine V or VI was produced by amination followed by cyclization of XI or XIX *via* isomerization of X or XVII, respectively, under the reaction conditions, although no isomerization was observed on the basis of the NMR and IR spectra under milder reaction conditions (80°C, 7 hr).

coal to give a colorless oil after the removal of the selvents. The oil was dissolved into acetone and diluted with water to give colorless needles of the monohydrate of V.

Cyclohexane-1-spiro-2'-(4'-oxopiperidine)-6'-spiro-1''-cyclohexane (VI). Similarly, a ketone mixture of XVII, XVIII, and XIX was treated for 24 hr. Almost pure crystals of VI separated out when the reaction mixture was cooled to room temperature.

Oxidation of Hindered Amine V with 30% Aqueous Hydrogen Peroxide in Methanol. The monohydrate of V(200 mg, 0.94 mmol) was oxidized with 0.5 g (4.41 mmol) of 30% aqueous hydrogen peroxide in 1 m*l* of methanol in the presence of EDTA and sodium tungstate at room temperature for 76 hr. After the removal of the methanol, 10 m*l* of benzene and 0.7 g of potassium carbonate were added to the reaction mixture; the resulting suspension was stirred at room temperature for 1 hr in order to decompose excess hydrogen peroxide. The potassium carbonate was filtered off; the subsequent evaporation of the benzene *in vacuo* gave *1-aza-2,2-dimethyl-4-oxo-spiro[5.5]undecane-1-oxyl (VII)* as an oil, which gave reddish needles upon recrystallization from *n*-hexane.
ESR: a triplet (10^{-3} M).

Oxidation of the Hindered Amine VI with 30% Aqueous Hydrogen Peroxide in Methanol. By the same procedures, the amine VI was recovered quantitatively. The oxidation of VI for 9 days gave a trace of the *N*-oxyl VIII, and most of the starting amine VI was recovered.

Cyclohexane-1-spiro-2'-(4'-oxopiperidine-1'-oxyl)-6'-spiro-1''-cyclohexane (VIII). A solution of 4.7 g (20 mmol) of the amine VI and 18.0 g (105 mmol) of CPBA in 120 m*l* of chloroform was stirred for 2 days at room temperature and washed with a 10% aqueous solution of potassium carbonate three times and then with water. The chloroform layer was dried over anhydrous magnesium sulfate and concentrated *in vacuo* to give a reddish oil, which solidified on being triturated in a small amount of petroleum ether. The crude product was dissolved into a small amount of benzene, after which petroleum ether was added to give reddish-orange prisms. ESR: a triplet (10^{-3} M).

The *N*-oxyl VII was also synthesized from V by similar procedures(CPBA).

The authors would like to thank Dr. Genshun Sunagawa, the director of these laboratories, for his encouragement and Mrs. Eiko Mori and Mr. Tsutomu Kanai for their technical assistance.