CHEMICAL REACTIONS OF 5-ALKYL-1,4-DIAZA- AND 5-ALKYL-1-AZA-4-OXABICYCLO[3.3.0]OCTAN-8-ONES

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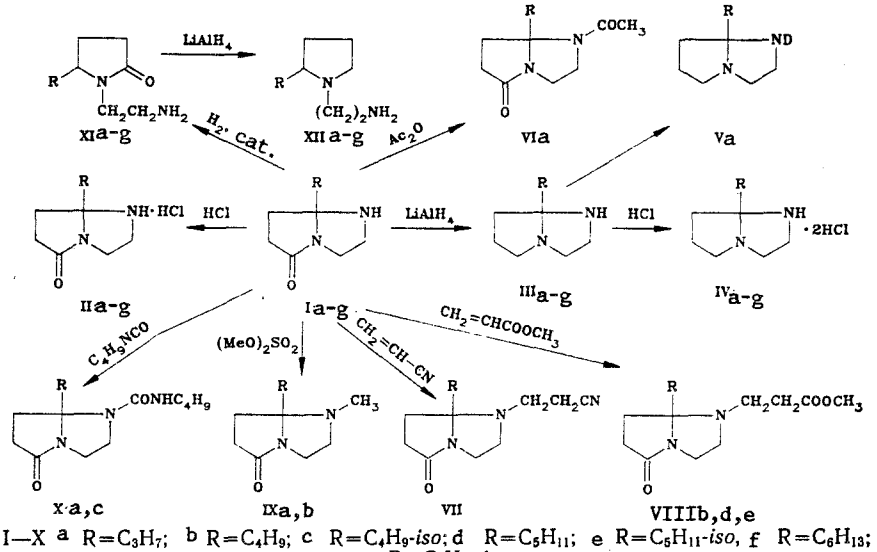
The behavior of 5-alkyl-1,4-diaza and 5-alkyl-1-aza-4-oxabicyclo[3.3.0]octan-8-ones has been studied towards catalytic reduction, reduction by lithium aluminum hydride, acylation, cyanoethylation, alkylation, etc. The oxazolidine ring in 5-alkyl-1-aza-4-oxabicyclo[3.3.0]octan-8-ones was readily opened by electrophilic and nucleophilic reagents whereas most of the reactions of 5-alkyl-1,4-diazabicyclo[3.3.0]octan-8-ones occurred with retention of the bicyclic structure.

We have previously reported [1] a convenient method for synthesizing 5-alkyl-1,4-diaza- and 5-alkyl-1-aza-4-oxabicyclo[3.3.0]octan-8-ones (Ia-g, XIIIa-e) but the chemistry of these groups of compounds has not been studied. This work has identified a significant difference in the chemical behavior of those compounds with nitrogen (Ia-g) and those with oxygen (XIIIa-e) at position 4 of the cicycle.

5-Alkyl-1,4-diazabicyclo[3.3.0]octan-8-one (Ia-g) contains an imidazolidine ring with an annelated 2-pyrrolidone ring. Although the ring in monocyclic imidazolidines is readily opened by the action of mineral acids or upon oxidation [2-4], compounds Ia-g were stable and the ring unbroken in the majority of the reactions studied. With dry hydrogen chloride in absolute ether Ia-g formed the hydrochlorides IIa-g. Reduction of Ia-g with lithium aluminum hydride gave IIIa-g which could then be converted to the dihydrochlorides IVa-g. For individual examples it was also shown that the 1,4-diazabicyclo[3.3.0]-octan-8-ones were acylated by acetic anhydride, reacted with acrylonitrile, methyl acrylate, or butyl isocyanate, and were methylated by dimethylsulfate to form VIa, VIIf, VIIIb,d,e, IXa,b, or Xa,c with retention of the bicyclic structure (Tables 1, 2).



I—X a R=C_3H_7; b R=C_4H_9; c R=C_4H_9-*iso*; d R=C_5H_{11}; e R=C_5H_{11}-*iso*, f R=C_6H_{13}; g R=C_6H_{13}-*iso*

The structures of IIIa, VIa, VIIf, Va, and XIIa were confirmed by ^{13}C NMR spectral data.

The ^{13}C NMR spectrum of IIIa (Table 3) showed the absence of a carbonyl carbon and the presence of a quaternary C_5 signal at 88.42 ppm. The presence of this signal, the C_5 peak in the 5-propyl-1,4-diazabicyclo[3.3.0]octane analog deuterated on nitrogen (Va) at 89.76

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TABLE 1. 5-Alkyl-1,4-diazabicyclo[3.3.0]octanes

Compound	bp, °C (10 mm Hg)	n_D^{20}	Found, %			Empirical formula	Calculated, %			Yield, %
			C	H	N		C	H	N	
IIIa	111—118	1,4755	70,4	11,6	18,0	$C_9H_{18}N_2$	70,2	11,8	18,2	67
IIIb	114—115	1,4770	71,6	11,9	17,7	$C_{18}H_{20}N_2$	71,5	12,0	16,7	70
IIIc	109—110	1,4760	71,2	11,9	16,5	$C_{10}H_{20}N_2$	71,5	12,0	16,7	74
IIId	110—113	1,4780	72,7	12,2	15,1	$C_{11}H_{22}N_2$	72,6	12,2	15,4	73
IIIe	114—116	7,4770	72,7	12,2	15,4	$C_{11}H_{22}N_2$	72,6	12,2	15,4	73
IIIf	120—121	1,4780	73,4	12,5	14,1	$C_{12}H_{24}N_2$	73,5	12,3	14,3	65
IIIg	118—120	1,4775	73,4	12,2	14,2	$C_{12}H_{24}N_2$	73,5	12,3	14,3	68

TABLE 2. 5-Alkyl-1,4-diazabicyclo[3.3.0]octan-8-ones

Compound	bp, °C (mm Hg)	n_D^{20}	Found, %			Empirical formula	Calculated, %			Yield, %
			C	H	N		C	H	N	
VIa	178—179(4)	1,5100	62,7	8,5	13,5	$C_{11}H_{18}N_2O_2$	62,9	8,6	13,3	83
VIIf	188—190(4)	1,5170	68,8	9,9	15,4	$C_{15}H_{25}N_3O$	65,9	9,2	15,3	60
VIIIb	153—155(10)	1,4970	62,6	9,0	10,4	$C_{14}H_{22}N_2O_3$	62,6	9,2	10,2	47
VIIId	165—167(10)	1,4990	64,2	8,5	10,1	$C_{15}H_{24}N_2O_3$	64,3	8,6	10,0	47
VIIIe	166—168(10)	1,4980	64,1	8,5	9,8	$C_{15}H_{24}N_2O_3$	64,3	8,6	10,0	50
IXa	139—141(9)	1,4750	65,8	9,8	15,2	$C_{10}H_{18}N_2O$	65,9	9,9	15,3	54
IXb	143—145(9)	1,4760	67,1	10,0	14,1	$C_{11}H_{20}N_2O$	67,4	10,2	14,2	50
Xa	153—155(10)	1,4980	62,9	9,2	15,5	$C_{14}H_{25}N_3O_2$	62,9	9,4	15,7	62
Xc	157—159(10)	1,4990	64,0	9,5	14,7	$C_{15}H_{27}N_3O_2$	64,1	9,6	14,9	60

TABLE 3. ^{13}C NMR Spectra of Ia, IIIa, Va, VIa, VIIf, XIIa

Compound	Chemical shift, δ, ppm								
	$C_{(2)}$	$C_{(3)}$	$C_{(5)}$	$C_{(6)}$	$C_{(7)}$	$C_{(8)}$	$C_{(9)}$	$C_{(10)}$	$C_{(11)}$
Ia	40,90	45,67	85,48	31,23	32,94	175,56	38,62	16,64	13,28
IIIa	53,22	42,91	88,42	42,07	22,95	53,87	35,33	16,75	13,05
Va	54,20	43,92	89,76	42,99	23,97	54,51	26,34	17,90	14,14
VIa	40,88	39,42	92,42	29,83	32,26	175,81	39,42	17,22	13,68
VIIf	41,02	45,70	85,68	31,23	33,10	165,74	38,69	16,79	13,40
XIIa	40,81	38,14	56,80	29,05	21,30	53,20	34,00	16,75	13,19

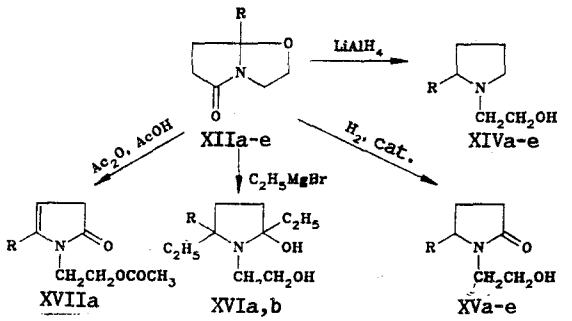
*For VIa C_{12} 171.61; C_{13} 22.85 ppm. For VIIf C_{12} 38.18; C_{13} 27.91; C_{14} 101.31 ppm.

ppm, and the absence of tertiary carbon signals in the off resonance spectrum pointed to the retention of the bicyclic structure. Reduction of the carbonyl group in Ia to methylene (IIIa) led to low field shifts of ~12 ppm for C_6 and C_2 and 3 ppm for C_5. Compound XIIa, being an analog of IIIa with reductive ring opening of the imidazolidine unit, was synthesized by [5] for spectral comparisons.

The ^{13}C NMR spectra of VIa and VIIf showed C_5 signals at 92.42 and 85.68 ppm which confirmed the presence of the bicyclic structure in the N-substituted 5-alkyl-1,4-diazabicyclo-[3.3.0]octan-8-ones.

Compounds Ia-g opened the imidazolidine ring only upon catalytic hydrogenation on Raney nickel at 120°C and a pressure of 10 mPa. The physical data for Xa-g was in full agreement with that for the same materials obtained previously by the alternative synthesis [5].

In contrast to Ia-g the oxa analogs 5-alkyl-1-aza-4-oxabicyclo[3.3.0]-octan-8-ones (XIIIa-e) were opened at the oxazolidine ring by lithium aluminum hydride reduction, catalytic hydrogenation, reaction with a Grignard reagent, and acylation with acetic acid or acetic anhydride. In the latter case there had been literature reports evidencing the N-acylation stabilization of the oxazolidine ring [6, 7].



XIII—XVII a R=C_3H_7; b R=C_4H_9; c R=C_4H_9-*iso*; d R=C_5H_{11}; e R=C_5H_{11}-*iso*

Compounds XIIIa-e and XIVa-e had been described previously [7, 8] and have been used as a reference materials for substance identification by GLC.

The reaction of XIIIa,b with ethylmagnesium bromide is a particular case of reductive alkylation with both opening of the oxazolidine ring and addition of the Grignard reagent to the carbonyl group. In the IR spectra of XVIa,b there were broad absorption bands at 3200-3400 cm^{-1} assigned to the associated hydroxyl group. Absorption of C=O in the region 1710-1720 cm^{-1} was not found. The Terentev method [9] indicated the presence of two hydroxyl groups.

Reaction of XIIIa with acetic acid or acetic anhydride also occurred with opening of the oxazolidine ring to give 5-propyl-2-oxo-1-(β-acetoxyethyl)pyrrol-2-ine (XVIIa). The double bond position was assigned using IR and PMR spectroscopy.

The IR spectrum of XVIIa showed a band near 1640 cm^{-1} for the non-conjugated C=C bond and the PMR spectrum a signal for one vinyl proton at 4.71 ppm.

Thus in the investigated bicyclic compounds XIIIa-e the oxazolidine ring was opened readily. Replacement of oxygen by nitrogen stabilized the ring and compounds Ia-g reacted with most of the reagents studied with retention of the bicyclic structure.

EXPERIMENTAL

Chromatographic analysis was carried out on an LKM-8MD instrument with flame ionization detector and a 0.6 cm (diameter) × 1 meter (height) stainless steel column. The sorbent was TND-TS-M grade brick modified by 2% KOH and impregnated with 15% Apiezon at 220-250°C. Helium carrier velocity 1.2 liter/h. IR spectra were recorded on a UR-20 instrument as paraffin mulls and capillary films. ^1H and ^{13}C NMR spectra were taken on a Varian RT-80 (80 MHz) instrument using $CDCl_3$ solvent and HMDS as internal standard.

5-Alkyl-1,4-diaza- and 5-alkyl-1-aza-4-oxabicyclo[3.3.0]octan-8-ones were prepared by condensation of ethyl ketocarboxylates with ethylenediamine and ethanolamine as described in [1].

5-Propyl-1,4-diazabicyclo[3.3.0]octan-8-one Hydrochloride (IIa). Dry HCl was passed for 30-40 min through a solution of Ia (1.68 g, 10 mmole) in absolute ether (20 ml) cooled to 0°C. The crystalline product was separated, washed with absolute ether (2 × 10 ml), and dried in vacuo to give (IIa) as white crystals (1.64 g, 80%) with mp 73-74°C. Found: Cl 17.6 %; N 13.5%. $C_9H_{17}ClN_2O$. Calculated: Cl 17.8; N 13.7%.

5-Alkyl-1,4-diazabicyclo[3.3.0]octanes (IIIa-g). A solution of Ia or Ig (20 mmole) in absolute ether (30 ml) was slowly dropped into a solution of ground lithium aluminum hydride (1.85 g, 50 mmole) in absolute ether (30 ml). The mixture was stirred at 40°C for 12-14 h and the reaction course followed by GLC. At the end of the reaction the excess hydride was decomposed by water (5 ml), the precipitate washed with ether (3 × 15 ml) and the combined ether extracts dried. Removal of ether by distillation and fractionation of the residue in vacuo gave IIIa with IR spectra bands (KBr) at 3330 and 3300 cm^{-1} (NH). The dihydrochloride of IIIa (IVa) occurred as white crystals with mp 53-54°C (from absolute ether). Found: Cl 31.2; N 12.4%. $C_9H_{20}Cl_2N_2$. Calculated: Cl 31.2; N 12.3%. Deuteration of IIIa according to [1] gave compound Va.

5-Propyl-4-acetyl-1,4-diazabicyclo[3.3.0]octan-8-one (VIa). A mixture of Ia (8.4 g, 50 mmole) and acetic acid (12 g, 100 mmole) or acetic anhydride was refluxed for 2-2.5 h, cooled and fractionated in vacuo. IR spectrum (KBr): 1720 (C=O lactam), 1680 cm^{-1} (C=O amide).

5-Hexyl-4-(N-cyanoethyl)-1,4-diazabicyclo[3.3.0]octan-8-one (VIIf). 5-Hexyl-1,4-diazabicyclo[3.3.0]octan-8-one (10.5 g, 50 mmole) and acrylonitrile (5.3 g, 100 mmole) were heated at 30-40°C for 2 h. The product was cooled and fractionated in vacuo. IR spectrum (KBr): 2225 (C≡N), 1710 cm^{-1} (C=O).

5-Alkyl-4-(β-carbomethoxyethyl)-1,4-diazabicyclo[3.3.0]octan-8-ones (VIIIb,d,e). Compound Ia (Ib or Id) (50 mmole) and methyl acrylate (4.3 g, 50 mmole) were refluxed in the presence of catalytic amounts of potassium hydroxide for 4 h. The product was fractionally distilled in vacuo. IR spectrum of VIIIa (KBr): 1718 (C=O lactam), 1740 (C=O ester), 1210 cm^{-1} (C–O–C ester).

5-Alkyl-4-methyl-1,4-diazabicyclo[3.3.0]octan-8-ones (IXa,b). Ia (Ib) (50 mmole) was slowly added to dimethyl sulfate (6.3 g, 50 mmole) in ether (20 ml) with cooling to 0°C and the mixture stirred for 2 h. It was adjusted to pH 7 with KOH solution (5%), the organic layer separated, and the aqueous layer extracted with ether (2 × 15 ml). The combined ether extracts were dried, ether removed, and the residue fractionated in vacuo. IR spectrum of IXa,b (KBr): 1770, 1700 cm^{-1} (C=O lactam).

5-Alkyl-4-butylamide-1,4-diazabicyclo[3.3.0]octan-8-ones (Xa,c). Ia (Ic) (30 mmole) and butyl isocyanate (4.95 g, 50 mmole) were heated in absolute toluene (50 ml) for 2.5 h at 140°C. Removal of solvent and distillation of the residue gave Xa. IR spectrum (KBr): 3300 (NH), 1700 (C=O lactam), 1680 cm^{-1} (C=O amide).

5-Alkyl-2,5-diethyl-2-hydroxy-N-(β-hydroxyethyl)pyrrolidine (XVIa,b). A solution of XIIIa (XIIIb) (30 mmole) in absolute ether (20 ml) was slowly dropped into a solution of the Grignard reagent (3.99 g, 30 mmole) prepared from Mg (1.68 g, 70 mmole) and C_2H_5Br (6.54 g, 60 mmole) and absolute ether (30 ml). The mixture was stirred at 20°C for 3 h, decomposed by water (15 ml), extracted with ether (3 × 10 ml), dried, and the residue after removal of solvent was fractionated in vacuo, XVIa (5.6 g, 67%) had bp 160-162°C (3 mm Hg) and n_D^{20} 1.4980. IR spectrum (KBr): 3400-3200 cm^{-1} (OH). Found: C 68.3; H 11.6; N 6.0%. $C_{13}N_{27}NO_2$. Calculated: C 68.2; H 11.9; N 6.1%. XVIb (5.2 g, 72%) had bp 167-168°C (3 mm Hg) and n_D^{20} 1.4990. IR spectrum (KBr): 3430-3200 cm^{-1} (OH). Found: C 69.0; H 11.6; N 5.4%. $C_{14}H_{29}NO_2$. Calculated: C 69.0; H 11.6; N 5.5%.

2-Propyl-5-oxo-1-(β-acetoxyethyl)pyrrol-2-ine (XVIIa). XIIIa (8.45 g, 50 mmmole) and CH_3COOH (6 g, 100 mmole) were refluxed for 2.5 h. Fractionation in vacuo gave the product (7.4 g, 87%) with bp 140-142°C (8 mm Hg) and n_D^{20} 1.4870. IR spectrum (KBr): 1720 (C=O lactam) 1745 (C=O), 1646 (unconjugated C=C), 1245 cm^{-1} (C–O–C).

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