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Studies on Azetidine Derivatives. IV.[1] Synthesis and Some Reactions of Azetidin-3-one Derivatives

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Although quite an extensive investigation has been done on azetidin-2-ones, only a few papers have been reported on azetidin-3-one derivatives. The compounds which fall in this category are 1-acetyl-2,2,4,4-tetramethylazetidin-3-one,[3] 1-benzoylazetidin-3-one[4] and 1-*t*-butyl-2,2-dimethylazetidin-3-one.[5] However no direct oxidation of 1-alkyl-azetidin-3-ols[6] to the corresponding azetidin-3-ones has been reported. This prompted us to attempt the oxidation of some 1-substituted-alkylazetidin-3-ols to the corresponding azetidin-3-ones which might be useful as intermediates in our studies exploring new azetidine derivatives.

Treatment of 1-diphenylmethylazetidin-3-ol (Ia)[7] with pyridine-SO_3 in DMSO and triethylamine for 30 min[8] gave 1-diphenylmethylazetidin-3-one (IIa) in good yield. The struc-

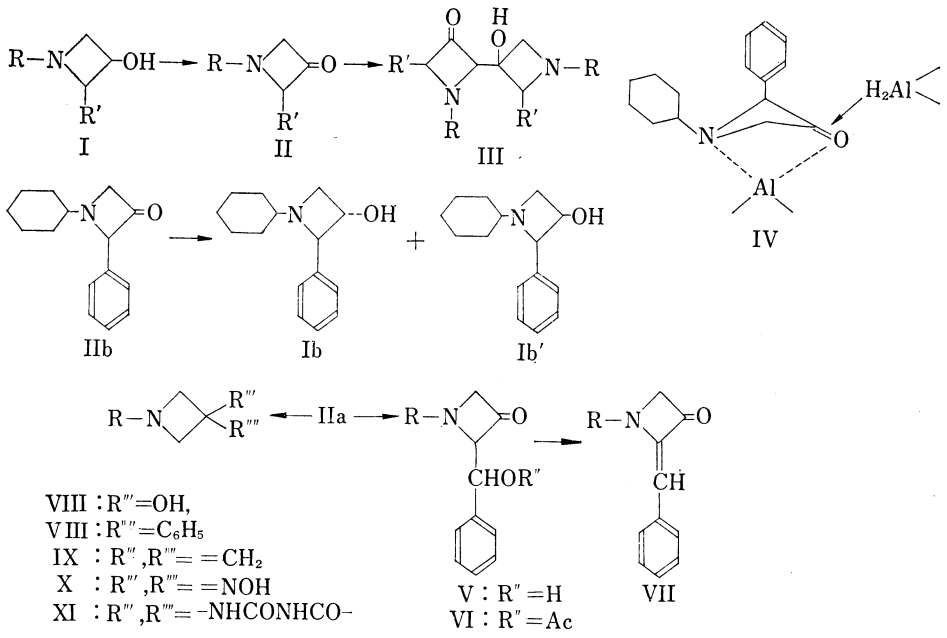

Chart 1

1) A part of this paper was presented at the 3rd International Congress of Heterocyclic Chemistry, Sendai, Aug. 23, 1971. Part III: T. Okutani, A. Morimoto, T. Kaneko, and K. Masuda, *Tetrahedron Letters*, **1971**, 1115.
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3) T. Chen, T. Sanjiki, and M. Ohta, *Bull. Chem. Soc. Japan*, **40**, 2397 (1967).
4) Scherico Ltd., Neth. Patent 6909923 (1969).
5) Eli Lilly and Company, U.S. Patent 346964 (1970) [*C. A.*, **70**, 987550w (1969)].
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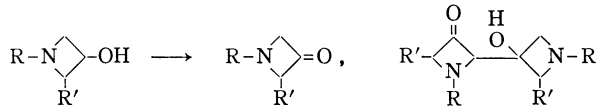
tural assignment of IIa was based on its spectral properties and conversion into the starting material (Ia) by $LiAlH_4$ reduction. Besides IIa was obtained a minor product which was characterized as a dimer (IIIa).

Similarly, 1-cyclohexyl-2-phenylazetidin-3-ol (Ib) (R: C_6H_{11}, R′: C_6H_5. R′ and OH are *trans*)[9] gave 1-cyclohexyl-2-phenylazetidin-3-one as an oily substance. The structure of IIb was confirmed by the $NaAlH_2(OCH_2CH_2OCH_3)_2$ reduction in benzene to give a mixture of *trans*- and *cis*-1-cyclohexyl-2-phenylazetidin-3-ols (Ib and Ib′) in 87% yield (*trans*: *cis*= 4: 1).[10]

TABLE I. Oxidation of 1-Substituted Azetidin-3-ols



I II III

Compound R	Compound R′	Product	mp (°C)	Yield (%)	IR ν_{max}^{Nujol} cm^{-1}	Formula	Analysis (%) Calcd. (Found) C	H	N	Mass spectra (M^+ *m/e*)
$(C_6H_5)_2CH$	H	IIa	77— 78	80	1805	$C_{16}H_{15}ON$	80.98 (80.96	6.37 6.36	5.90 5.90)	237
		IIIa	174—175	16	3500—3400 1810	$C_{32}H_{30}O_2N_2$	80.98 (80.69	6.37 6.56	5.90 5.83)	474
Cyclohexyl	C_6H_5	IIb	oil	67	1805	$C_{15}H_{19}ON$	78.56 (78.12	8.35 8.65	6.11 6.51	229
t-C_4H_9	H	IIIc	76— 77	1.5	3400—3000 1800	$C_{14}H_{26}O_2N_2$	66.10 (65.92	10.30 10.71	11.01 10.95)	254
Cyclohexyl	H	IIId	100—101	33	3500—3000 1800	$C_{18}H_{30}O_2N_2$	70.55 (70.29	9.87 9.84	9.14 9.05)	306
$C_6H_5CH(CH_3)$	H	IIIe	oil	30	3400—3200 1802	$C_{22}H_{26}O_2N_2$	75.40 (75.15	7.48 7.10	7.99 8.31)	350

In general, it is well known that the metal hydride reduction of α-hydroxy and α-amino ketones proceeds with a relatively high degree of stereoselectivity. The reason for this stereoselectivity has been attributed to the initial formation of a complex which is further attacked by the metal hydride from the less hindered side.[11] Thus the predominant formation of the *trans* isomer (Ib) is explicable by the hydride attack from the least hindered side of the carbonyl group as depicted in the Chart (IV).

When 1-*t*-butylazetidin-3-ol (Ic), 1-cyclohexylazetidin-3-ol (Id) and 1-(α-methylbenzyl)-azetidin-3-ol (Ie) were oxidized under similar conditions, the corresponding dimers IIIc, IIId and IIIe were obtained almost exclusively as summarized in the Table.

1-Diphenylmethylazetidin-3-one (IIa) is stable when stored at room temperature, but in methanol solution it is easily converted into the dimer (IIIa) when heated at 50° for 24 hr. On the other hand when a methanol solution of IIa was heated at 50° for 24 hr in the presence of benzaldehyde the Aldol condensation product, 1-diphenylmethyl-2-(α-hydroxybenzyl)-azetidin-3-one (V), was obtained exclusively. Acetylation of V with acetylchloride and triethylamine in benzene yielded 1-diphenylmethyl-2-(α-acetoxybenzyl)azetidin-3-one (VI), which on heating at 170° for 2 min gave 1-diphenylmethyl-2-benzylidenazetidin-3-one (VII).

9) A mixture of Ib and Ib′ was prepared by the treatment of 2-bromo-3-chloro-1-hydroxy-1-phenylpropane with two molar equivalents of cyclohexylamine in DMSO at 50—60° for 20 hr. Each isomer was purified by column chromatography. Details will be published elsewhere.

10) The stereochemistry of the isomers (Ib and Ib′) has been described in our previous paper.[1]

11) D.J. Cram and D.R. Wilson, *J. Am. Chem. Soc.*, **85**, 1245 (1963).

The utility of IIa for the preparation of various azetidine derivatives was investigated. The carbonyl group of IIa underwent a variety of the carbonyl group reactions; for example, upon treatments with phenylmagnesium bromide, triphenylphosphinemethylene, or hydroxylamine there were obtained 1-diphenylmethyl-3-hydroxy-3-phenylazetidine (VIII) (as hydrochloride), 1-diphenylmethyl-3-methylenazetidine (IX), or 1-diphenylmethyl-3-hydroxyiminoazetidine (X) in good yield, respectively. Treatment of IIa with potassium cyanide and ammonium carbonate in aqueous alcohol at 110° gave spiro-(1-diphenylmethylazetidine-3,5′-hydantoin) (XI).

From these results it is evident that azetidin-3-ones serve as useful intermediates leading to various azetidine compounds which are otherwise difficult to attain.

Experimental[12]

General Procedure of the Oxidation of 1-Alkylazetidin-3-ols (I)——To a solution of DMSO (80 ml) containing 1-alkylazetidin-3-ol (I) (30 mmole) and triethylamine (30 g) was added pyridine-SO_3 complex (30 g) in DMSO (140 ml) with stirring at room temperature. After stirring for 30 min the reaction mixture was poured into ice water. The resulting oil was extracted with ethyl acetate, washed with water and dried over anhydrous magnesium sulfate. The residue obtained by the evaporation of the solvent was submitted to purification by chromatography on silica gel eluted with benzene and ethyl acetate. The results are summarized in the Table.

Reduction of 1-Diphenylmethylazetidin-3-one (IIa) with $LiAlH_4$——To a solution of $LiAlH_4$ (40 mg) in tetrahydrofuran (5 ml) was added a solution of IIa (237 mg) in tetrahydrofuran (5 ml). The reaction mixture was stirred for 30 min at room temperature and an excess of $LiAlH_4$ was decomposed with ether saturated with water. The solid was filtered off and washed with tetrahydrofuran. The combined filtrate was dried over anhydrous potassium carbonate and evaporated to give 227 mg (95%) of crystalline substance which was identified with Ia by the comparison of infrared (IR) and nuclear magnetic resonance (NMR) spectra.

Reduction of 1-Cyclohexyl-2-phenylazetidin-3-one with $NaAlH_2$ $(OCH_2CH_2OCH_3)_2$——To a solution of IIb (229 mg) in benzene (5 ml) was added $NaAlH_2$ $(OCH_2CH_2OCH_3)_2$ (600 mg of 70% benzene solution) at room temperature. After stirring for 2 hr the reaction mixture was washed with water and dried over anhydrous magnesium sulfate. Removal of the solvent gave 200 mg (87%) of crystalline substance. The NMR spectrum of this crystalline substance showed that it is *ca.* a 4:1 mixture of *trans*- and *cis*-1-cyclohexyl-2-phenylazetidin-3-ols.[10]

1-Diphenylmethyl-2-(α-hydroxybenzyl)azetidin-3-one (V)——A mixture of Ia (400 mg) and benzaldehyde (400 mg) in methanol (5 ml) was stirred at 50° for 24 hr. After cooling the precipitates were collected and recrystallized from ethyl acetate–ether to give 250 mg (43%) of V, mp 147—148°. *Anal.* Calcd. for $C_{23}H_{21}O_2N$: C, 80.44; H, 6.16; N, 4.08. Found: C, 80.26; H, 6.14; N, 3.85. IR ν_{max}^{Nujol} cm^{-1}: 1807 (C=O).

1-Diphenylmethyl-2-(α-acetoxybenzyl)azetidin-3-one (VI)——To an ice-cooled solution of V (2.20 g) and triethylamine (1.00 g) in benzene (20 ml) was added acetylchloride (0.700 g) during 5 min. The reaction mixture was stirred for 2 hr and then washed with water and dried over anhydrous magnesium sulfate. Removal of the solvent under reduced pressure followed by crystallization from ether afforded 1.20 g (51%) of VI, mp 145—148° (decomp.). *Anal.* Calcd. for $C_{25}H_{23}O_3N$: C, 77.90; H, 6.01; N, 3.63. Found: C, 77.97; H, 5.93; N, 3.73. IR ν_{max}^{Nujol} cm^{-1}: 1805 (C=O) and 1713 ($OCOCH_3$).

1-Diphenylmethyl-2-benzylidenazetidin-3-one (VII)——VI (365 mg) was heated at 170° for 2 min without solvent. After cooling the reaction product was crystallized from ether to give 204 mg (63%) of VII, mp 124—125°. *Anal.* Calcd. for $C_{23}H_{19}ON$: C, 84.89; H, 5.89; N, 4.30. Found: C, 84.91; H, 5.89; N, 4.24. IR ν_{max}^{Nujol} cm^{-1}: 1770 (C=O). NMR ($CDCl_3$): δ 3.90 (2H, singlet, CH_2), 5.06 (1H, singlet, CH–N), 5.28 (1H, singlet, –CH=C), 7.00—7.60 (15H, multiplet, aromatic).

1-Diphenylmethyl-3-hydroxy-3-phenylazetidine (VIII)——To a solution of phenylmagnesium bromide (430 mg) in ether (15 ml) was added a solution of Ia (574 mg) in ether (15 ml) at 5° with stirring and the mixture was stirred for 1 hr. The reaction mixture was decomposed with water, then washed with water and dried over potassium carbonate. Removal of the solvent gave an oil (689 mg, 91%) of VIII. Treatment of VIII with methanol-HCl afforded the hydrochloride of VIII, mp 196—197°. *Anal.* Calcd. for $C_{22}H_{22}ONCl$: C, 75.07; H, 6.30; N, 3.98. Found: C, 74.91; H, 6.23; N, 3.99.

1-Diphenylmethyl-3-methylenazetidine (IX)——To a solution of triphenylphosphinemethylene prepared from triphenylmethylphosphonium bromide (5.60 g) and potassium *t*-butoxide (1.68 g) in DMSO

12) All the melting points were uncorrected. Nuclear magnetic resonance (NMR) spectra were measured with a Varian HA-100 spectrometer using tetramethylsilane as an internal standard.

(20 ml) was added a solution of Ia (1.19 g) in DMSO (10 ml) and the mixture was heated at 60° for 24 hr. The reaction mixture was poured into ice water and extracted with ether, washed with water and dried over anhydrous potassium carbonate. The solvent was removed *in vacuo* and the residue was recrystallized from *n*-pentane to give 906 mg (75%) of IX, mp 73—74°. *Anal.* Calcd. for $C_{17}H_{17}N$: C, 86.77; H, 7.28; N, 5.95. Found: C, 86.69; H, 7.28; N, 5.91. NMR ($CDCl_3$): δ 3.72 (4H, triplet, $J=2$ cps, CH_2NCH_2), 4.41 (1H, singlet, CH), 4.80 (2H, quartet, $J=2$ cps, $=CH_2$), 7.00—7.50 (10H, multiplet, aromatic).

1-Diphenylmethyl-3-hydroxyiminoazetidine (X)——To a solution of Ia (1.00 g) and hydroxylamine hydrochloride (500 mg) in ethanol (20 ml) was added a solution of sodium hydroxide (500 mg) in water (2 ml) and the mixture was heated at 80° for 15 min. The reaction mixture was poured into water and neutralized with acetic acid. The resulting precipitates were collected and dried. Recrystallization from ether gave 1.03 g (97%) of X, mp 169—170°. *Anal.* Calcd. for $C_{16}H_{16}ON_2$: C, 76.16; H, 6.39; N, 11.10. Found: C, 76.14; H, 6.36; N, 11.22. NMR ($CDCl_3$): δ 3.94 (4H, quartet, $J=4$ cps, CH_2NCH_2), 4.51 (1H, singlet, CH), 7.10—7.45 (10H, multiplet, aromatic), 7.78 (1H, singlet, N-OH).

Spiro-(1-diphenylmethylazetidine-3,5′-hydantoin) (XI)——A mixture of Ia (1.20 g), potassium cyanide (0.65 g) and ammonium carbonate (1.92 g) in 50% ethanol (20 ml) was stirred at 110° in a sealed tube for 15 hr. After cooling the reaction mixture was poured into water and the resulting precipitates were collected and dried. Recrystallization from ethanol gave 465 mg (34%) of (XI), mp 238—240°. *Anal.* Calcd. for $C_{18}H_{17}O_2N_3$: C, 70.34; H, 5.58; N, 13.67. Found: C, 70.31; H, 5.49; N, 13.71. IR ν_{max}^{Nujol} cm^{-1}: 3250 (NH) and 1730 (NHCO). NMR (d_6-DMSO): δ 3.20 and 3.40 (4H, two doublets, $J=8$ cps, CH_2NCH_2), 4.46 (1H, singlet, CH), 7.00—7.50 (10H, multiplet, aromatic), 9.50 and 11.57 (2H, two singlets, NHCONH).

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Studies on Microbial Transformation. XXVI.[1] Microbial Oxidation of (−)-Sparteine

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The successful establishment of the application of microorganisms to the synthesis of biologically active steroids has awaken the interest in the field of microbial conversion of various alkaloids, and hence the systematic investigations of yohimbine-,[3] steroid-,[4] ergot-,[5] and morphine-[6] alkaloids have been carried out in the last decade.

Although lupin alkaloid is one of the large groups in alkaloid kingdom, only one transformation of the compound of this type, *i.e.*, a microbial transformation of (+)-lupanine

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