SYNTHESIS OF SUBSTITUTED TETRAHYDRO-1,3-OXAZINES

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UDC 547.867.2.07

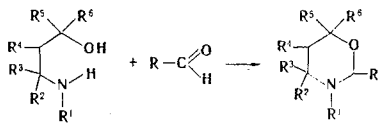
A number of mono-, di-, tri-, and tetrasubstituted tetrahydro-1,3-oxazines were synthesized by the reaction of 3-amino- and 3-methylamino-1-propanols with aldehydes.

In recent years tetrahydro-1,3-oxazines and their functional derivatives have been attracting the attention of investigators in connection with the diverse physiological activity of compounds of this class [1]. Some tetrahydro-1,3-oxazine derivatives are effective vulcanization accelerators [2].

The establishment of the configurations and conformations of substituted tetrahydro-1,3-oxazines, which is one of the chief stages in the elucidation of the interrelationship between their structure and activity, is extremely important for the realization of the directed search for new physiologically active substances and effective vulcanization accelerators. For this purpose, we undertook the synthesis and investigation of the three-dimensional structure of substituted tetrahydro-1,3-oxazines by PMR spectroscopy. The presence of two heteroatoms in the 1and 3 positions of the ring of the investigated compounds makes it possible to use the PMR spectra extremely effectively not only to establish their configurations [3] and conformations [4] but also to determine the orientation of the unshared pairs of electrons of the heteroatoms [5, 6].

The most general method for the preparation of substituted tetrahydro-1,3-oxazines is condensation of 3-amino- and 3-alkylamino-1-propanols with aldehydes [7-11], but the absence of simple and convenient methods for the preparation of the starting γ-amino alcohols has up to now substantially restricted the use of the indicated method.

In the present paper we describe the preparation of a number of previously unknown mono-, di-, and polysubstituted tetrahydro-1,3-oxazines (II) by cyclization of substituted 3-amino- or 3-methylamino-1-propanols (I) with formaldehyde and benzaldehyde.



I II

Aminopropanols I recently became readily accessible owing to our development of simple and convenient methods for the synthesis of α- and β-substituted alkyl and phenyl β-aminoalkyl ketones [12, 13] and their N-alkyl derivatives [14] from α,β-unsaturated ketones. The reaction of these amino ketones with lithium aluminum hydride leads to substituted amino alcohols I (R^1 = H, CH_3; R^2, R^3, and R^4 = H, CH_3; R^5 = H, CH_3, C_2H_5, C_6H_5; R^6 = H) with a secondary hydroxyl group, while reaction with Grignard reagents leads to the analogs of I (R^1 = CH_3; R^2 = R^3 = H; R^4, R^5 = CH_3; R^6 = C_2H_5) with a tertiary hydroxyl group [15]. Amino alcohols I (R^1, R^4 = CH_3; R^2 = R^3 = H; R^5 = R^6 = CH_3, C_2H_5, C_6H_5) with a tertiary hydroxyl group

M. V. Lomonosov Moscow Institute of Precision Chemical Engineering. V. I. Ul'yanov-Lenin State University. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 4, pp. 467-471, April, 1973. Original article submitted March 17, 1972.

TABLE 1

Compound	R	R¹	R²	R³	R⁴	R⁵	R⁶	bp, °C (mm)	n_D^{20}	R_f [a]	Compound	Retention time, min	mp of the hydrochloride, °C	Empirical formula	Found, % C	Found, % H	Found, % N	Calc., % C	Calc., % H	Calc., % N	Yield, %
IIa	H	CH_3	H	H	CH_3	CH_3	H	51—52 (80)	1,4351	0,8	IIa	5,3	186—187 b	$C_7H_{15}NO$	64,9	11,5	11,3	65,1	11,7	10,8	52
IIb	H	CH_3	H	H	CH_3	H	H	85—86 (130)	1,4425	0,9				$C_7H_{15}NO \cdot HCl$	50,5	9,3	8,4	50,8	9,7	8,5	
IIc	H	H	CH_3	CH_3	H	CH_3	H	72—73 (50) [7]	1,4395	0,6	IIb	5,0	190—191 c	$C_7H_{15}NO$	64,8	11,6	10,8	65,1	11,7	10,8	68
IId	H	CH_3	CH_3	CH_3	H	CH_3	H	72—73 (60)	1,4428	0,78				$C_7H_{15}NO \cdot HCl$	51,2	9,9	8,4	50,8	9,7	8,5	
IIe	H	CH_3	CH_3	H	CH_3	CH_3	H	92—93 (50)	1,4479	0,9	IIc	5,5	152—153 b	$C_7H_{15}NO \cdot HCl$	51,0	9,6	8,4	50,8	9,7	8,5	70
IIf	H	CH_3	CH_3	H	CH_3	CH_3	H	45—46 (90)	1,4450	0,85	IId	7,0	—	$C_8H_{17}NO$	67,2	11,9	9,8				67
IIg	H	CH_3	H	H	H	C_6H_5	H	109—110 (15) [22]	1,5283	0,8	IIe	7,1	—	$C_8H_{17}NO$	67,2	12,0	10,3	67,1	12,0	9,8	48
IIh	H	CH_3	H	H	CH_3	C_6H_5	H	100—101 (25)	1,5288	0,67	IIf	6,3	—	$C_8H_{17}NO$	67,2	11,8	9,8				32
IIi	H	CH_3	CH_3	H	H	C_6H_5	H	80—82 (1)	1,5225	0,65	IIg	22,0	163—164 c	$C_{11}H_{15}NO \cdot HCl$	61,5	7,6	6,4	61,8	7,5	6,5	85
IIj	H	CH_3	H	H	H	H	H	34—36 (7)	1,4512	0,85	IIh	22,5	181—182 c	$C_{12}H_{17}NO \cdot HCl$	63,7	7,9	6,1	63,5	8,0	6,2	72
IIk	C_6H_5	CH_3	H	H	CH_3	H	H	110—112 (23)	1,5192	0,90	IIi	35,0	183—184 b	$C_{12}H_{17}NO$	75,4	9,2	7,4	75,3	9,0	7,3	70
IIl	H	CH_3	H	H	CH_3	CH_3	CH_3	69—70 (20)	1,4432	0,85	IIj	6,2	155—156 b	$C_8H_{19}NO \cdot HCl$	47,4	9,5	9,3	47,3	9,3	9,2	70
IIm	H	CH_3	H	H	CH_3	C_2H_5	C_2H_5	64—65 (5)	1,4620	0,80	IIk	19,1	—	$C_{12}H_{17}NO$	75,8	9,3	7,9	75,3	9,0	7,3	58
IIn	H	CH_3	H	H	CH_3	C_2H_5	C_6H_5	—	—	0,8	IIl	7,0	—	$C_8H_{17}NO$	67,0	11,9	10,1	67,1	12,0	9,8	80
IIo	H	CH_3	H	H	CH_3	C_6H_5	C_6H_5	64—66 (8)	1,4532	0,62	IIm	9,0	194—195 c	$C_{10}H_{21}NO \cdot HCl$	57,7	10,7	6,4	57,8	10,7	6,7	85
														$C_{10}H_{21}NO$	70,5	12,4	8,3	70,1	12,4	8,2	
											IIn	—	120,5—121,5 d	$C_{18}H_{21}NO$	81,0	8,0	5,2	80,9	7,9	5,2	89
											IIo	13,2		$C_{10}H_{17}NO$	71,4	10,0	8,2	71,8	10,2	8,3	83

a) In ether; b) from acetone–alcohol; c) from acetone; d) this is the melting point of the base crystallized from hexane.

and identical substituents attached to the carbonyl carbon atom were in turn synthesized from Grignard reagents and methyl β-methylacetamidoisobutyrate (III) which was obtained by acetylation of methyl β-methylaminoisobutyrate [16]; their analogs with a primary hydroxyl group I (R^1, R^4 = CH_3; R^2 = R^3 = R^5 = R^6 = H) were synthesized by reduction of amino ester III with lithium aluminum hydride.*

Cyclization of amino alcohols I with formaldehyde and benzaldehyde, which leads to substituted tetrahydro-1,3-oxazines II in yields of 60-90%, proceeds with different degrees of ease depending on the structure of the starting substances. When R^5 = R^6 = H, CH_3, C_2H_5, the condensation of amino alcohols I with formaldehyde proceeds readily and rapidly at room temperature without a solvent, while when R^5 = R^6 = C_6H_5, the reaction is carried out in alcoholic media in the presence of potassium carbonate [17]. The condensation of amino alcohols I with benzaldehyde proceeds with considerably greater difficulty and requires refluxing of a mixture of the starting substances in toluene and continuous removal of the water liberated in the reaction [18]. According to the results of gas-liquid chromatography (GLC), in a number of cases the compounds obtained contained a small amount of the corresponding bis(tetrahydro-1,3-oxazin-2-yl)-methane, and the material was purified by adsorption chromatography with columns containing aluminum oxide. The properties and yields of the synthesized bases of the substituted 3-methyltetrahydro-1,3-oxazines (II) or their hydrochlorides are presented in Table 1.

In conformity with [19], the cyclization of amino alcohols I, which contain chiral centers in the 1 and 2 positions, proceeds without a change in the steric arrangement of the substituents in the 1 position; this is confirmed by cleavage of oxazines II with lithium aluminum hydride [19], which leads to starting compounds I.

We established the configurations and preferred conformations of the synthesized tetrahydro-1,3-oxazines by means of the PMR spectra. As an example, we present the analysis of the PMR spectra of 3,4-dimethyl-6-phenyl- and 3,4,6-trimethyltetrahydro-1,3-oxazines (IIh and IIb). From the PMR spectrum of oxazine IIh (Fig. 1), one can unambiguously conclude that the 4-CH_3 and 6-CH_3 groups are equatorially oriented from the magnitude of the spin-spin coupling constants of the vicinal protons (J_{4a5a} = 11.0 Hz and J_{5a6a} = 10.7 Hz) [20]. The spatial orientation of the methyl group attached to the nitrogen atom of IIh was determined from the magnitude of J_{2a2e}. It is known

*We will describe the syntheses of the substituted 3-amino- and 3-methylamino-1-propanols (I) in a separate communication.

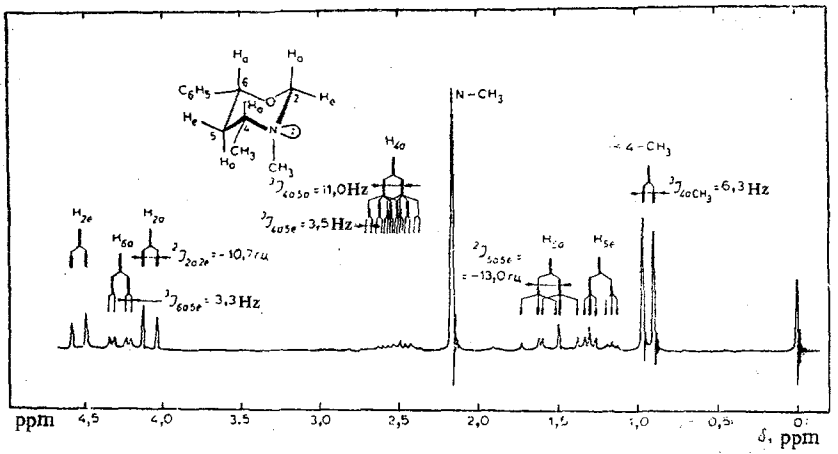


Fig. 1. PMR spectrum of 3,4,6-trimethyltetrahydro-1,3-oxazine.

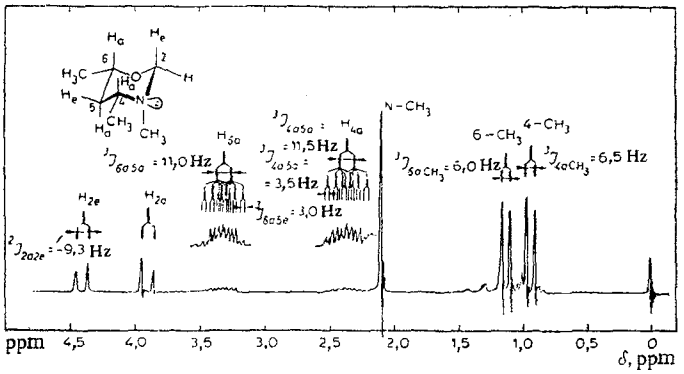


Fig. 2. PMR spectrum of 3,4-dimethyl-6-phenyltetrahydro-1,3-oxazine.

[21] that J_{2a2e} for tetrahydro-1,3-oxazines in the "chair" conformation depends on the spatial orientation of the methyl group attached to the nitrogen atom and the p orbital of the unshared pair of electrons of the latter, which proves to be − 7.7 Hz for the equatorial and − 10.5 Hz for the axial [21] orientation of the methyl group attached to nitrogen. In IIh, the J_{2a2e} value of − 10.7 Hz attests to an axial orientation of the methyl group attached to the nitrogen atom and to an equatorial orientation of its unshared pair of electrons. Thus, according to the PMR spectrum, IIh has the preferred "chair" conformation with 3*a*4e6e orientation of the substituents in the ring.

Similarly, it follows from the PMR spectrum of IIb (Fig. 2), that J_{6a5a} and J_{4a5a} have values of 10.0 and 11.0 Hz, respectively; this attests to an equatorial orientation of the methyl groups in the 4 and 6 positions of the tetrahydrooxazine ring. In [21], from the J_{2a2e} value of − 9.3 Hz, it was concluded that the methyl group attached to the nitrogen atom is axially oriented; this is also confirmed by a study of the effect of an aromatic solvent on the relative chemical shifts of the protons. It follows from these data that IIb has the preferred "chair" conformation with a 3*a*4e6e orientation of the methyl substituents in the 4 and 6 positions. We used a similar route to establish the three-dimensional structures of all of the remaining oxazines (II).

EXPERIMENTAL

Analytical GLC was carried out with an LKhM-7A chromatograph: the detector was a katharometer, the column (3 m by 6 mm) was filled with 10% polyethylene glycol on Chromosorb P (60-80 mesh), the carrier gas was helium, the gas flow rate was 70 ml/min, and the column temperature was 110° for IIa-f, IIj-m, and IIo and 170° for IIg-i and IIn. The retention times are presented in Table 1. Thin-layer chromatography was carried out on plates with a loose layer of activity-II aluminum oxide in ether and ether–hexane (1 : 1) with development of the chromatograms with iodine vapors. The PMR spectra of 10-20% solutions of the compounds in CCl_4 were measured with an NA-100D spectrometer with tetramethylsilane as the internal standard.

3,5-Dimethyl-6,6-diethyltetrahydro-1,3-oxazine (IIm). A total of 6 ml (0.08 mole) of 40% aqueous formaldehyde was added by drops in the course of 10 min at 15-20° to 5.68 g (0.03 mole) of 5-methylamino-4-methyl-3-ethyl-3-pentanol. The mixture was then cooled to room temperature, saturated with potassium carbonate, and extracted with 200 ml of ether. The ether extracts were dried with magnesium sulfate, and the ether was removed to give 6.0 g of liquid oxazine IIm with R_f 0.6, which contained a small amount of an impurity with R_f 0.1. The purification of 3 g of oxazine IIm was carried out with a chromatographic column 500 mm long and 18 mm in diameter) containing 200 g of activity II aluminum oxide (chromatography grade) with ether as the eluent. The first 500 ml of eluate yielded 2.5 g of oxazine IIm with R_f 0.6, which was converted to the hydrochloride with mp 194-195° (from acetone).

Tetrahydro-1,3-oxazines IIa-f, IIj, IIl, ^{Hz}and IIo were similarly obtained.

3,5-Dimethyl-6,6-diphenyltetrahydro-1,3-oxazines (IIn). A total of 33 ml (0.45 mole) of a 40% aqueous solution of formaldehyde was added in the course of 15 min to a solution of 10.34 g (0.39 mole) of 3-methylamino-2-methyl-1,1-diphenyl-1-propanol in 70 ml of alcohol containing 5 g of potassium carbonate, after which the mixture was stirred at room temperature for 1 h and extracted with ether (three 150-ml portions). The ether extracts were combined, washed with 150 ml of water, and dried with magnesium sulfate. Removal of the ether gave 9.31 g of crystalline oxazine IIn.

Tetrahydro-1,3-oxazines IIg-i were similarly obtained.

3,5-Dimethyl-2-phenyltetrahydro-1,3-oxazine (IIk). A 10.7-g sample (0.1 mole) of benzaldehyde was added to a solution of 10.0 g (0.097 mole) of 3-methylamino-2-methyl-1-propanol in 200 ml of anhydrous toluene, and the mixture was then refluxed for 2 h with a reflux condenser fitted with a Dean–Stark trap until 1.8 ml of water had separated. Vacuum distillation gave 10.8 g of oxazine IIk with bp 110-112° (23 mm).

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