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OXAZOLIDINES.

BASIC CATALYTIC DISPROPORTIONATION OF CYCLOHEXANOSPIRO-1. 2-OXAZOLIDINES: SYNTHESIS OF N-SUBSTITUTED 4,5,6,7-TETRAHYDROINDOLES

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It has been shown that the basic catalytic disproportionation of cyclohexanospiro-2-oxazolidines in the presence of potassium hydroxide or sodium methylate leads to N-substituted 4,5,6,7-tetrahydroindoles with a yield of up to 73%. The influence of the character of substituents at the nitrogen atom of oxazolidine on the course of the reaction has been established.

The cyclohexanospiro-2-oxazolidines disproportionate in the presence of potassium tertbutylate to form tetrahydroindole derivatives with yields of up to 20% [1]. In order to develop a procedure for the preparation of 1-substituted tetrahydroindoles from readily availably cyclohexanospiro-2-oxazolidines we have investigated the disproportionation of 3-(2-hydroxyethyl)-cyclohexanospiro-2-oxazolidine (I) under the influence of the hydroxides and alcoholates (C1-C4) of potassium, sodium, lithium, calcium, barium, and aluminum. The highest activity (at a high selectivity) was shown among the catalysts of this series by potassium hydroxide and sodium methylate, while the aluminum hydroxide and alcoholates did not catalyze the process at all. The highest yields of 1-(2-hydroxyethy1)-4,5,6,7-tetrahydroindole (IIa) (63-73%) were obtained by refluxing 1 mole of oxazolidine I with 0.2-0.5 mole potassium hydroxide or sodium methylate. The duration of the reaction, determined by GLC from the time required for the complete decomposition of the oxazolidine Ia, was 2.5-4 h.

The disproportionation of the oxazolidines Ib-m was also performed under the conditions found.



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Com-	bp [mp], °C	d	11 4 1 40	Found, %			Empirical	Calculated, %			Yield,
	(prostate, mm)			- 63	11	N	formula	- (₁	11	N	%
IIA IIb IIc IId IIf IIf IIf IIf IIf IIf IIf IIf IIf	$\begin{array}{c} 144-147 \ (5) \\ 103-104 \ (11) \\ 115-118 \ (20) \\ 114-117 \ (5) \\ 116-118 \ (12) \\ 110-112 \ (9) \\ 152-155 \ (5) \\ 150-152 \ (4) \\ 134-137 \ (3) \\ 150-153 \ (4) \\ 133-134 \ (3) \\ 113-116 \ (15) \\ [33-34] \end{array}$	$\begin{array}{c} 1.0801\\ 0.9906\\ 0.9566\\ 0.9469\\ 0.9441\\ 0.9465\\ 1.0736\\ 1.0736\\ 1.0548\\ 1.0067\\ 1.0601\\ 1.0310 \end{array}$	$\begin{array}{c} 1,5413\\ 1,5287\\ 1,5135\\ 1,5100\\ 1,5081\\ 1,5081\\ 1,5960\\ 1,5960\\ 1,5756\\ 1,5330\\ 1,5360\\ 1,5360\\ 1,5257\end{array}$	72,3 70,3 81,2 81,0 81,1 85,4 85,4 85,4 85,4 85,4 85,4 85,4 85,4	$\begin{array}{c} 9.3\\ 9.6\\ 10.6\\ 10.5\\ 10.9\\ 10.6\\ 7.6\\ 8.0\\ 10.5\\ 9.6\\ 9.9\\ 10.7\end{array}$	$\begin{array}{c} 8.7\\ 10.2\\ 8.5\\ 8.0\\ 7.9\\ 7.1\\ 6.6\\ 7.0\\ 7.6\\ 7.1\\ 9.5\end{array}$	СраН ₁₂ NO СраН ₁₃ N СтаНа7N СтаНа7N СтаНа2N СтаНа2N СтаНа2N СтаНа2N СтаНа2N СтаНа2N СтаНа2N СтаНа2N СтаНа2N СтаНа2N СтаНа2N СтаНа2N СтаНа2N	$\begin{array}{c} 72.6\\ 80.0\\ 80.9\\ 81.3\\ 81.3\\ 85.2\\ 85.3\\ 82.7\\ 73.7\\ 74.6\\ 80.5\end{array}$	9.2 9,7 10,5 10,8 10,8 10,8 7,7 8,1 10,4 9,9 10,1	8.5 10.4 8.6 7.9 7.9 7.9 7.9 7.9 7.9 7.9 7.9 7.9 7.9	73 72 36 47 30 38 42 59 68 58

TABLE 1. Tetrahydroindoles Ia-m

Besides the tetrahydroindoles IIa-m, cyclohexanols and aminoalcohols are also formed in the reaction with yields of 75-95%. The character of the substituent at the nitrogen atom of the oxazolidine ring has an essential influence on the course of the process. Thus the time required for the complete conversion (as controlled by GLC) of 3-methyl- (Ib), 3-benzyl- (Ih), and 3-phenylcyclohexanospiro-2-oxazolidines (Ig) to the corresponding tetrahydroindoles in the presence of 40 mole % of potassium hydroxide was 3,5,8, and 15 h, respectively; 3-acetylcyclohexanospiro-2-oxazolidine could not be converted to the corresponding indole in the presence of the above amount of catalyst even when heated at 250° for 20 h. Attempts to disproportionate cyclohexanospiro-2-oxazolidine and 5-methylcyclohexanospiro-2-oxazolidine, unsubstituted at the nitrogen atom, lead to their complete decomposition, accompanied by the formation of cyclohexanol, ethanol- and propanolamines (respectively), and resin-like substances; only traces of the expected 4,5,6,7-tetrahydroindole and 3-methyl-4,5,6,7-tetrahydroindole were detected. Such a strong difference in the behavior of the N-substituted and N-unsubstituted oxazolidines can only be attributed to the fact that the latter, inclining to tautomerism, react not in the cyclic form but in the form of azomethyne alcohols instead.

Thus, the region in which the reaction of basic catalytic disproportionation proceeds normally is limited on one side by the N-unsubstituted oxazolidines and on the other side by oxazolidines containing a low-basicity, for instance, an amide nitrogen atom. Within this region the reaction can be used successfully for the preparative synthesis of N-substituted 4,5,6,7-tetrahydroindoles.

The identity and structure of the synthesized tetrahydroindoles IIa-m have been confirmed by GLC and IR and NMR spectroscopy. The physicochemical constants of the cyclohexanols and aminoalcohols obtained in the reactions correspond to literature data.

EXPERIMENTAL

The cyclohexanospiro-2-oxazolidines used in the work were synthesized by the condensation of cyclohexanone and 2-methylcyclohexanone with aminoalcohols according to the procedure given in [2]. The chromatographic analysis was performed on a LKhM-8MD chromatograph equipped with a catharometer detector; the length of the column was 2 m, the diameter 3 m; the solid phase was Chromaton N-AW-HMDS, the liquid phase 15% DS-550 siloxane oil; temperature programming was used from 100 to 225°C at a rate of 4°/min, with helium as the carrier gas. The NMR (PMR) spectra were taken on a BS-487B spectrometer (80 MHz). The compounds were investigated as 10-% solutions in CC14 with HMDS as internal standard. The IR spectra were obtained on a UR-20 spectrometer in the form of liquid films or KBr tablets.

<u>General Procedure for the Disproportionation of Cyclohexanospiro-2-oxazolidines.</u> A mixture of 0.2 mole of oxazolidine Ia-m and 0.04-0.1 mole potassium hydroxide or sodium methylate is brought to the boil. The initial boiling temperature $(220^{\circ}-260^{\circ})$ decreases gradually and spontaneously to 150-260°. Samples are taken periodically during the reaction (1-2 times per hour) and analyzed by GLC. The reaction is continued until complete conversion of the oxazolidine. The cooled reaction mixture is dissolved in 200 ml benzene and extracted with water $(3 \times 50 \text{ ml})$; the extract is distilled in vacuum to separate cyclohexanol and the 4,5,6,7tetrahydroindoles. The aminoalcohols are isolated from the combined aqueous extracts. In the disproportionation of oxazolidines Ig-i ethanolamines are formed which are poorly soluble in water. The benzene solution of the reaction mixture is treated first with the calculated

			PI	MR spe	IR spectrum, ν , cm ⁻¹			
Com- pound	2-H	3-Н d	4-H, 7-H M	5-H, 6-H m	R	pyrrole ring	=CH	R
IIa	6,3, d*	5,65	2,41	1,71	3,53, m (NCH ₂ CH ₂ O), 2,75, s (OH)	1490, 1570, 1660	3090	3440 (OH)
IIb IIc	6,15, d 6,40,d	5,64 5,77	$2,34 \\ 2,50$	1,67 1,75	3,20, s (NCH ₃) 4,05, m (NCH), 1,29, d	1485, 1570 1490, 1580,	3090 3110	(0.1)
IId	6,30, d	5,66	2,44	1,61	$(CH_3)C(H_3)$ 3,53, t (NCH ₂), 1,42 1,61, m (CH ₂ CH ₂), 0,90, t	1485, 1620	3095, 3118	
li1e	6,23, d	5,62	2,42	1,60— 1,70	(CH ₃) 3,42, d (NCH ₂), 1,40— 1,95, m (CCHC), 0,92, d	1500, 1590, 1640	3100	
IIf	6,30,đ	5,67	2,42	1,60— 1,70	$(1, CH_3, CCH_3)$ (3, 80, m) (NCH), $(1, 55 - 1, 90)$ (CCH ₂ C), $(1, 30, d)(NCCH_2) (0, 77)$	1485, 1580, 1640	3100, 3125	
IIg	6,55, d	5,87	2,55	1,75	(NCCCH ₃) (NCCCH ₃) 7,23, m (C ₆ H ₅)	1500, 1590	3055, 3070,	
IIh	6,31, d	5,80	2,35	1,66	4,71, s (NCH ₂), 7,14, m (C ₆ H ₅)	1490, 1670	3100 3030, 3065, 3095	1590, 1602 (CoHc)
Hi	6,32, d	5,65	2,49	1,43-	3,65, m (NCH), 1,43—	1480, 1662	3085,	(06115)
IIk	6,33, d	5,69	2,40— 2,57	1,75	$(CH_2)_5$ 3,60, m (NCH_2CH_2O), 3,15, s (OH), 1,14, d	1492, 1560, 1642	3120 3100	3450 (OH)
11.1	6,09,s		2,35	1,77	(OCH_3) 3,52, d (NCH ₂), 3,71,m (OCH), 3,40, s (OH); 1.85 s (C-CCH-) 1.20	1520	3100	3420 (OH)
IIm	6,05,s	—	2,40	1,74	$\begin{array}{c} 1, 0, 0 \\ d \\ (OCCH_3) \\ 3.25, s \\ (C=CCH_3) \end{array}$	1530, 1590, 1630	3060, 3110	

TABLE 2. Spectroscopic Characteristics of Tetrahydroindoles Ia-m

*SSIC ${}^{2}J_{23} = 2.9 \pm 0.1$ Hz in all compounds.

amount of 1 mole/liter hydrochloric acid and then extracted with water (3×50 ml); the extract is washed with 100 ml 1% sodium carbonate solution and distilled. The quantity of acid is taken which is necessary to neutralize the catalyst and 0.1 mole of the aminoalcohol formed. The aminoalcohol is isolated from the combined extracts (after neutralization with potassium hydroxide) by distillation in vacuum.

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