REACTIONS OF 1-VINYL-4,5,6,7-TETRAHYDROINDOLE AND ITS MIXTURES WITH 4,5,6,7-TETRAHYDROINDOLE IN THE PRESENCE OF Cr- AND Pd-COATED CATALYSTS

> M. A. Ryashentseva, Yu. B. Vol'kenshtein, V. M. Polosin, A. I. Mikhaleva, and R. N. Nesterenko

In the presence of Cr- and Pd-coated γ -alumina catalysts, l-vinyl-4,5,6,7-tetrahydroindole (VTHI) and its mixtures with 4,5,6,7-tetrahydroindole (THI) are converted into l-ethyl-4,5,6,7-tetrahydroindole (l-ETHI), indole, and 2-ethylindole, in proportions dependent on the reaction conditions and the catalyst. Over a sulfided 1% Pd- γ -alumina catalyst in the presence of hydrogen at 200°C, VTHI is converted into l-ETHI and THI. When the temperature is raised to 300-350°C, indole is formed in addition to these products. A 1:1 mixture of VTHI and THI over 1% Pd- γ -alumina at 300°C gives indole and 2-ethylindole, over a sulfided 1% Pd- γ -alumina catalyst at 200°C, l-ETHI, and over a Cr oxide catalyst at 500°C, indole.

N-Vinylpyrroles have now become readily available thanks to the development of a simple method of preparation from ketoximes and acetylene by the Trofimov reaction [1]. With cyclohexanone oxime, the reaction affords THI and VTHI:



Under the optimum conditions, VTHI is obtained in 83-93% yields [2, 3]. Both THI and VTHI are prospective indole synthons [1, 4], especially for the preparation of difficultly accessible α -substituted indoles [5, 6].

We have examined the reactions both of VTHI and of its crude mixtures with THI over Pd- and Cr-oxide catalysts in order to assess the possibility of the catalytic synthesis of indole and its derivatives.

EXPERIMENTAL

The reactions of VTHI and its mixtures with THI in a solvent (benzene or toluene) were carried out in a through-flow apparatus at atmospheric pressure and a temperature of 200-525°C, $V_{mass} = 0.3-1.2$ h⁻¹, duration of experiments 0.5-3 h. Alumina-platinum catalysts containing 1 and 1.5% Pd on commercial γ -alumina with a specific surface area of 200-220 m²/g, granule size 2 × 3 mm, were used. Reduction was carried out at 350°C, and sulfidation with hydrogen sulfide at 120°C. The preparation of a chromic oxide catalyst with percentage composition Cr₂O₃ 5, Polirit 5, K₂O 1, and γ -alumina 89 has been described [7].

The VTHI had bp 85-86°C (3 mm), d_4^{20} 1.001, n_D^{20} 1.5562, and the mixtures contained (wt. %) 31.3 VTHI and 68 THI, and 48.6 VTHI and 49.7 THI, the remainder being cyclohexanone oxime (obtained from cyclohexanone oxime and acetylene in a pilot plant [1] and used without separation as being the most readily available technical tetrahydroindole-containing material). The benzene, toluene, and cyclohexane were chemically pure grade.

N. D. Zelinskii Institute of Organic Chemistry, Academy of Sciences of the USSR, Moscow. Irkutsk Institute of Organic Chemistry, Siberian Branch, Academy of Sciences of the USSR. Translated from Izvestiya Akademii Nauk SSSR, Seriya Khimicheskaya, No. 6, pp. 1417-1422, June, 1991. Original article submitted June 29, 1990. TABLE 1. Reactions of VTHI in Toluene over Hydrogen Sulfide-Treated Pd- γ -Alumina Catalysts*

unt of I in Lene, %	Expe	eriment litions	al	d of . cata- te, %	Comp lyza	ositio te, wi	on of (t. %	cata-	Yield based on VTHI introduced/ reacted, wt. %			
Amou VTH tolu wt.	T, °C	V _{mass} , h ⁻¹	τ , min	Yiel liq lyza wt.	VTHI	THI	1- ETHI	in- dole	THI	1- ETHI	indole	
				1% P	d/γ-Al ₂	O3, H2S	3					
21,2	200	0,9	30	80,4	61,2	15,3	23,5	-	10,5	17,0	-	
21,2	250	0,9	30†	96,0	64,7	18,8	16,5	-	19,0 16,5	30,9 14,2	-	
25,8	3 00	0,9	30	80,0	10,7	24,5	55,2	9,6	36,8 17,0	31,6 39,8	8,0	
25.8	350 ‡	1.0	30+	91.1	30.7	22.9	39.8	6.6	18,3 18,3	42,7	8,5	
2010		110			00,1			0,0	$\frac{10,8}{24,7}$	45,1	7,3	
$1.5\% \text{ Pd}/\gamma - \text{Al}_2\text{O}_3, \text{H}_2\text{S}$												
23,5	2 00	1,0	30	82,7 ‡	56,2	9,3	28,7	'	6,7	21,3		
23,5	250	1,0	30 †	95,6 ‡	29,4	20,6	42,9		11,5 14,6 18,8	36,3 37,0 47.9	•	
		1			3							

*Hydrogen introduced at a rate of 2.6 liters/h. +Over the same catalyst sample, the temperature being raised by 50°C.

#Unidentified peaks amounted to ~6%.

The starting materials and the catalyzates were analyzed on an LKhM-8MD gas chromatograph (catharometer, 110-250°C, 12 deg/min), columns 2000 × 3 mm, 3% OV-225 on Chromaton N-Super (0.125-0.161 mm) and 3 × 1500 mm, 2% OV-225 on Chromosorb G (0.147-0.175 mm) at 190°C, carrier gas helium.

The indole was separated from the catalyzate by TLC (hexane-ethyl acetate, 6:1). Found, Z: C 82.05; H 6.14; N 12.09. C₆H₇N. Calculated, Z: C 82.0; H 6.02; N 11.96. The structure of the indole was proved by PMR and mass spectrometry. The PMR spectrum was obtained on a Bruker WM-250 spectrometer, operating frequency 250 MHz, and mass spectra on a Varian MAT-311A mass spectrometer, ionizing voltage 70 eV. 2-Ethylindole was isolated by TLC, and identified by ¹H and ¹³C NMR, mass spectrometry, and GLC. The chromatographic peaks were identified using pure VTHI, 1-ETHI, THI, indole, and 2- and N-ethylindole. The chromatograms were measured by area.

The results are shown in Tables 1-3 and Scheme 1.

RESULTS AND DISCUSSION

The choice of a Pd catalyst for the reactions of VTHI and of its mixtures with THI was based on reported results [8-10], in which it was shown that in the case of cyclohexane in benzene a 0.5% Pd-y-alumina catalyst treated with hydrogen sulfide had considerable dehydrogenation activity. The use of Cr oxide catalysts in these reactions was also of interest, since a previously developed catalyst of this type was found to possess considerable dehydrogenation activity [11]. There has been a report [12] of the effects of additives in alumina-chromium catalysts of composition (%): Cr_2O_3 5, La_2O_3 5, K_2O 1, and γ -alumina 89 in the reaction of H_2S and C_4 -hydrocarbons. The γ -alumina carrier has cracking and hydrogenating properties, and the chromic oxide dehydrogenating, hydrogenating, heterocyclizing, and cracking properties. The lanthanum and potassium oxides promote the heterocyclizing and dehydrogenating activity, and reduce the cracking and carbonizing effects of the alumina catalyst. This catalyst is highly active in the synthesis of thiophene from C4-hydrocarbons and H2S, and is resistant to the poisoning effects of sulfur. The lanthanum oxide in this mixture was later replaced by Polirit, a mixture of rare-earth oxides [7]. The dehydrogenating activity of this catalyst was first assessed in the reaction with cyclohexane. At T 525-550°C and Vmass 0.9 h⁻¹, the yields of benzene were 72 and 80% on cyclohexane introduced, respectively. Under these conditions, benzene and toluene were unaffected.

uene (T)	in the Pr	esen	ce of	Cr-	and P	d-Coated	γ-Al	umina	Cataly	stsa					
Composi-	Amount of	Sol-	Expt	.1. cond	litions	Yield of	-	Cataly	yst comp	osition,	wt. %		Yie	ld based wt. %	ио
initial mixture, wt. %	mixture in solution, wt. %	vent	Ŀ	C Vmass h ⁻¹	T, min	catalyzate wt. %	IHIV	THI 1	-ethyl- ndole	indole	2-ethyl- indole	uniden- tified products	1-ethy1- indole	indole	2-ethyl- indole
and and the second s	and a second						Cr o	kide							
31.3 VTHI 68.0	53,1 53,8 51,9	<u>а</u> е е	 2888	55 0.5 0.5 1.0 1.0	 868	89,9 73.6 82,9	2:1	20.2 Iraces	1364	50,2 80,9 82,9	12.1 4,8 8,9	8.6 5.8 5.8	4,9 1,0 1,0	44,6 58,1 65,7	10,7 3,4 6,8
THI 48,6 VTHI VIII	2000 2000 2000 2000 2000 2000 2000 200	ma ⊱ ⊱ ÷	2222	50 0.3 0.3 0.3 0.3 0.3 0.3 0.3 0.3 0.3 0.	3888	84,5 86,8 b 84,6 b 82,6 b	- 21	504- 504-	0,00 % r 0,00 % r	64,4 50,7 79,4	12,8 23,5 8,2 8,2 8,2 8,2 8,2 8,2 8,2 8,2 8,2 8,2	11.5 15.9 7.5	4 -9 5	54,3 40,2 59,8 59,0	10.5 3,0 5,4 5,4
THT PAD					<u>ne</u>	5 6'06	1% D(1.1.1 1/7-Al ₂ O ₃	2		-) j		5
18.6 VTHI 7.7 THT	24.7 24.7 23,5		350 350 350 350	0.5 	666 8888	82.75 87.75 88.74 87.74 87.74 87.74	1 0 3 8 0 1	3.4	312 0 1 312 4 0 32 2 4 0	50.8 50.8 43.4 47.3	33.7 30.2 34,1 34,1	9.6 9.6 10,0	2,67 2,67 2,67 2,67 2,67 2,67 2,67 2,67	35,5 47,2 33,7 37,2	23,5 23,7 22,5 26,8
		4	-	-	-	4	r								

Reactions of Mixtures of Tetrahydroindole and 1-Vinvltetrahydroindole in Benzene (B) and Tol-TARLE 2

^aHeating of catalyst and experiment in nitrogen, 3.6 liters/h. ^bHeating in nitrogen, experiment without carrier gas. ^cHeating and experiment in hydrogen, 3.6 liters/h. ^dExperiment with same sample of catalyst without hydrogen. ^eExperiment with the same sample of catalyst as in the preceding experiment.

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TABLE 3. Reactions of a Mixture of 48.6% VTHI and 49.7% THI in Toluene over Palladium-Alumina Catalysts Treated with Hydrogen Sulfide, in Hydrogen

Amount	Ex	ptl.		Yield of	Cat	alyza	te com	Yield d	of 1-			
of ini-	<u></u> co	<u>nditior</u>	ETHI, wt. %									
tialmix- ture in soln., wt. %	Τ,°C	V _{mass} , h ⁻¹	τ, min	alyzate, wt. %	VTHI	THI	1- ETHI	unidenti fied products	based on initial mixture	based on VTHI reacted		
			1%	$Pd/\gamma - \Lambda l_2O_3$. ∙trea	ted wi	th H ₂ S					
$\begin{array}{c c} 25.1 \\ 25.1 \\ 22.0 \\ 26.3 \\ 26.3 \\ 24.4 \\ 24.4 \\ 36.2 \\ 36.2 \\ 9.4 \\ 9.4 \\ \end{array}$	$\begin{array}{c} 200\\ 250\\ 200\\ 250\\ 300\\ 350\\ 200\\ 250\\ 200\\ 250\\ 200\\ 250\\ 200\\ 250\\ 25$	$ \begin{array}{c} 0.5 \\ 0.5 \\ 1.0 \\ 1.2 \\ 1.2 \\ 0.5 \\ 0.5 \\ 0.5 \\ 0.5 \\ 0.5 \\ 0.5 \\ 0.5 \\ 0.5 \\ 0.5 \\ 0.5 \end{array} $	$\begin{array}{c c} 30 \\ 60 \\ 30 \\ 60 \\ 90 \\ 120 \\ 30 \\ 60 \\ 90 \\ 120 \\ 130 \\ 130 \\ 180 \\ 180 \\ \end{array}$	84,9 97,6 81,0 86,3 94,8 90,7 76,9 86,3 79,9 86,3 79,9 89,5 99,0 90,8	$\begin{array}{c} 10,5\\ 2,4\\ 5,6\\ 4,9\\ 7,9\\ 2,0\\ 2,3\\ 7,2\\ 2,7\\ 14,9\\ 5,8 \end{array}$	$\begin{array}{c} 61,4\\ 59,1\\ 67.7\\ 59.8\\ 61,2\\ 60,8\\ 56,6\\ 53,0\\ 63,4\\ 57,7\\ 66,9\\ 59,6\\ \end{array}$	$\begin{array}{c} 28,1\\ 38,5\\ 26,7\\ 35,0\\ 30,5\\ 23,3\\ 41,4\\ 39,8\\ 29,4\\ 39,4\\ 18,3\\ 33,5\\ \end{array}$	$ \begin{array}{c} - \\ 0,3 \\ 0,3 \\ 7,2 \\ - \\ 4,9 \\ 0,2 \\ 1,1 \end{array} $	$\begin{array}{c} \textbf{21,5} \\ \textbf{33,8} \\ \textbf{19,4} \\ \textbf{27,0} \\ \textbf{26,4} \\ \textbf{19,0} \\ \textbf{27,9} \\ \textbf{30,8} \\ \textbf{21,4} \\ \textbf{32,2} \\ \textbf{16,0} \\ \textbf{28,0} \end{array}$	52,8 72,9 44,0 57,2 45,7 59,1 65,9 50,0 70,0 44,8 64,1		
			1.5%	, Pd/γ - Al_2O_2	, trea	ted wit	th Π_2 S					
25,8 25,8 25,7 25,7	$rac{200}{250} \\ rac{200}{200} \\ rac{200}{200} \end{cases}$	0.5 0.5 1.0 1.0	30 60 30 60	86, 1 93,2 84,5 92,3	$\begin{array}{c} 3.0 \\ 0.9 \\ 6.8 \\ 1.8 \end{array}$	51.6 48.9 49.3 57.0	43,2 44,9 41,5 37,0	2,3 5,3 2,3 4,3	$37.2 \\ 37.6 \\ 31.5 \\ 30.1$	$\begin{array}{c} 83.4 \\ 92.5 \\ 71.0 \\ 63.6 \end{array}$		

As	shown	in	Table	1,	1-ETHI,	THI,	and	indole	are	formed	from	VTHI	(Scheme	1)	:
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Scheme 1



For example, VTHI over sulfided 1% Pd/ γ -alumina at 200°C, V_{mass} 0.9 h⁻¹, 30 min in a stream of hydrogen (3.6 liters/h) affords 30.9% 1-ETHI and 19.0% THI, i.e., hydrogenation of the vinyl C=C and cracking of VTHI occur, with hydrogenolysis of the N-C bond. The other cracking products range from 5 to 20%. When the reaction temperature is raised to 300°C, the yield of 1-ETHI rises to 42.7%. In addition to these reactions, dehydrogenation of the cyclohexane ring also occurs to give indole (7.1%). Increasing the concentration of palladium to 1.5%, at temperatures of 200 and 250°C and V_{mass} 1.0 h⁻¹ results in an increase in hydrogenation and a decrease in cracking, the yields of 1-ETHI reaching ~37%. It is noteworthy that over γ -alumina treated with H₂S, at 200°C 1-ETHI and THI are also formed, in yields of 3.0 and 1.6%, respectively. 1-ETHI has been obtained previously in 90% yield by hydrogenation of VTHI over Raney nickel in ethanol under a hydrogen pressure of 40-60 atm [13].

As will be seen from Tables 2 and 3, the main reaction products from mixtures of VTHI and THI are, depending on the catalyst used, 1-ETHI, indole, and 2-ethylindole. Over a chromic oxide catalyst, two mixtures containing 31 and 49% VTHI (the remainder being THI) at 500-525°C, V_{mass} 0.3-1.5 h⁻¹ afforded indole as the main product, the amounts in the catalyzate reaching 83%. VTHI also undergoes hydrogenation of the vinyl group to give 1-EI and migration of the ethyl group to the α -position of the pyrrole ring to give 2-EI. The yield of the latter reaches 18.4% (the thermal isomerization of 1-alkylpyrroles to the 2alkyl compounds is well known [14]).

This catalyst has been found to have isomerizing activity with respect to (benzo[b]thien-2-yl)silans at 550-560°C [15].

The use of benzene or toluene as solvent has little effect on the formation of 1- and 2-ethylindoles. When the feed rate of VTHI was increased from 0.5 to 1.5 h⁻¹, a maximum was seen at which the yield of indole reached 65.7%, at 525°C and V_{mass} 1.0 h⁻¹. Increasing T from 500 to 525°C increased the yield of indole from 44.6 to 65.7% while reducing the yield of 1-EI and 2-EI from 4.8 to 1.0 and 10.7 to 6.8%, respectively.

The catalyst maintained its high dehydrogenating activity in the formation of indole from VTHI over a period of 60 min. Whether the reaction was carried out in nitrogen or hydrogen had no effect on the dehydrogenation reaction.

When 1% Pd/ γ -alumina was used as catalyst, the VTHI underwent the same reactions as over the chromic oxide catalyst, but less severe conditions were required. At 360°C, V_{mass} $0.5 h^{-1}$, 47.2% of indole was obtained, while the amount of 2-ethylindole increased by more than twofold as compared with the catalyzate obtained over the chromic oxide catalyst, but l-ethylindole was absent. The formation of 2-ethylindole is probably due to the high acidity of the γ -alumina, which facilitates the migration of the ethyl group to the α -position of the pyrrole ring, as compared with its acidity in the chromic oxide catalyst. Its lower acidity in the latter is apparently due to the oxide additives Cr_2O_3 , rare earths, and K_2O . The main factor in determining the course of these reactions over the palladium-alumina catalyst is the temperature. The volume feed rate of the mixture, and the reaction times, have little effect on the yields of indole and 2-ethylindole.

The selectivity of the sulfided palladium-alumina catalyst is, as will be seen from Table 3, very different from that of the palladium-alumina catalyst. Over a sulfided 1% Pd/ γ -alumina catalyst, a 1:1 mixture of VTHI and THI gives 1-ETHI only, i.e., hydrogenation of the vinyl group occurs. At 250°C, V_{mass} 0.8 h⁻¹, over 60 min, the yield of 1-ETHI in the mixture is 33.8%, or 72.9% on VTHI reacting. Increasing T to 350°C does not result in any significant increase in the yields of 1-ETHI, in contrast to the results obtained with pure VTHI. These results show that the presence of THI in the initial mixture has an effect on the catalysis. The addition of solvent in amounts of (mixture:solvent) 9.4, 24.4, and 36.2% at 200-250°C and V_{mass} 0.5 h⁻¹ had no effect on the selectivity of the catalyst after three hours' operation.

Increasing the concentration of palladium to 1.5% resulted in a marked increase in the hydrogenating ability of the catalyst. The yield of 1-ETHI at 250°C, V_{mass} 0.5 h⁻¹, 60 min was 37.6% (92.5% on VTHI reacting).

It is thus possible to direct the reactions of VTHI and its mixtures with THI toward the formation of 1-ETHI and indole, or a mixture of indole and 2-ethylindole, by choice of the appropriate catalyst. For example, over a sulfided 1.5% Pd/ γ -alumina catalyst (T 250°C, V_{mass} 1.0 h⁻¹), VTHI affords 47.9% of 1-ETHI, while a 1:1 mixture of VTHI and THI (T 250°C, V_{mass} 0.5 h⁻¹) gives 37.6% of 1-ETHI. Over a 1% Pd- γ -alumina catalyst (T 350°C, V_{mass} 0.5 h⁻¹), this mixture afforded 47.2% of indole and 23.7% of 2-ethylindole, while a chromic oxide catalyst (T 525°C, V_{mass} 0.3 h⁻¹, 30 min) gave 60.8% of indole. These latter results showing the formation of indole from mixtures of VTHI and THI indicate that the cyclohexane ring in both VTHI and THI undergoes dehydrogenation.

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REACTION OF METHYL 3-PHENYL-3-CHLORO-2-OXOPROPIONATE WITH THIOSEMICARBAZONES

> V. A. Mamedov, V. N. Valeeva, L. A. Antokhina, and I. A. Nuretdinov

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The reaction of methyl 3-phenyl-3-chloro-2-oxopropionate with thiosemicarbazones proceeds via the intermediate formation of methyl [S-(1'-alkylideneisothiosemicarbazidyl)]-3-phenyl-2-oxopropionate hydrochlorides, which then cyclize to novel 4-methoxycarbonyl-5-phenyl-2-substituted thiazoles. Hydrolysis of the intermediate products and the thiazoles obtained therefrom with simultaneous distillation of the carbonyl compound affords 2-hydrazino-4-methoxycarbonyl-5-phenylthiazole.

There have been literature reports of the synthesis of thiazoles from thioamides [1] and thiosemicarbazides [2, 3], but the use of thiosemicarbazones for this purpose has received less attention. Continuing studies of the reactions of α -chloroketones with bifunctional compounds [4, 5], we here describe the reactions of methyl-3-phenyl-3-chloro-2-oxo-propionate (I) with thiosemicarbazones.

Condensation of the α -chloroketone (I) with thiosemicarbazones occurs in two stages. The first of these, formation of the intermediate methyl [S-(l'-alkylideneisothiosemicarbazidyl)]-3-phenyl-2-oxopripionate hydrochlorides (II), occurs under mild conditions, namely on mixing equimolar amounts of the reactants at ~20°C in a solvent (acetone or CCl₄).



A. E. Arbuzov Institute of Organic and Physical Chemistry, Kazan Science Center, Academy of Sciences of the USSR. Translated from Izvestiya Akademii Nauk SSSR, Seriya Khimicheskaya, No. 6, pp. 1422-1426, June, 1991. Original article submitted July 4, 1990.