SYNTHESIS OF 5-n-ALKYL-2-(trans-4-n-ALKYLCYCLOHEXYL)PYRIDINES

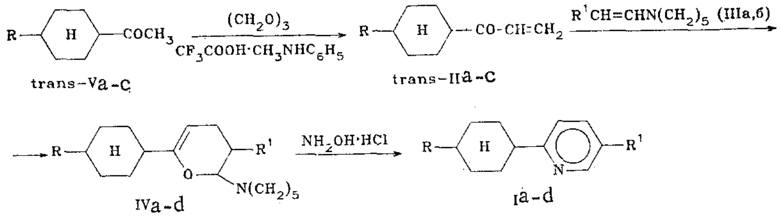
A. I. Pavlyuchenko, G. V. Purvanetskas,
V. K. Daukshas, N. I. Smirnova,
N. I. Korotkova, and E. I. Kovshev

UDC 547.822

The cyclization of trans-1-acrylyl-4-n-alkylcyclohexanes with trans-1-N-piperidino-1-alkenes was used to synthesize 3-n-alkyl-6-(trans-4-n-alkylcyclohexyl)-3,4-dihydro-2-N-piperidino-2H-pyrans, which were converted under the influence of hydroxylamine to 5-n-alkyl-2-(trans-4-n-alkylcyclohexyl)-pyridines. Problems in the stereochemistry of the cyclohexane derivatives in the investigated scheme of synthesis were examined.

In connection with the search for new components of liquid-crystal materials that have low viscosity we studied the possibility of obtaining previously undescribed 5-n-alkyl-2-(trans-4-n-alkylcyclohexyl)pyridines. Cyclohexyl-substituted pyridines are difficult to obtain. A method for their preparation with the aid of organolithium derivatives of pyridine is known [1].

We have investigated the possibility of the preparation of 5-n-alkyl-2-(4-n-alkylcyclohexyl)pyridines (I) by diene condensation of 1-acrylyl-4-n-alkylcyclohexanes (II) with 1-N-piperidino-1-alkenes (III) and subsequent conversion of the resulting 3-n-alkyl-6-(4-n-alkylcyclohexyl)-3,4-dihydro-2-N-piperidino-2H-pyrans (IV) to pyridines I.



I, IV a $R=H$, $R^1=C_2H_5$; b $R=H$, $R^1=C_3H_7$; c $R=C_4H_9$, $R^1=C_2H_5$; d $R=C_6H_{13}$, $R^1=C_3H_7$;
II, V a $R=C_4H_9$; b $R=C_6H_{13}$; c $R=H$; III a $R^1=C_2H_5$; b $R^1=C_3H_7$

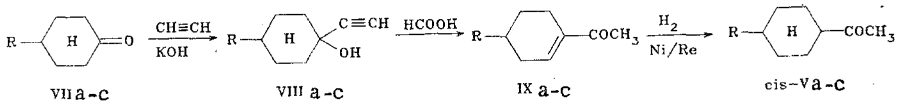
The indicated scheme was previously used [2] in the synthesis of 2-methyl-5-isobutylpyridine.

Starting enamines IIIa,b (previously described in [3]) were obtained by condensation of aliphatic aldehydes with piperidine in the presence of potassium carbonate and, judging from the spin–spin coupling constant (SSCC) of the vinyl protons (J = 14 Hz) in the PMR spectra, are trans isomers.

Vinyl ketones IIa-c were synthesized by the reaction of 4-n-alkyl-1-acetylcyclohexanes (V) with trioxymethylene in the presence of N-methylaniline trifluoroacetate by the method previously proposed for the preparation of acrylylcyclohexane [4].

trans-4-n-Alkyl-1-acetylcyclohexanes Va-c were obtained by the catalytic reaction of trans-4-n-alkylcyclohexanecarboxylic acids (VI), which were described in [5], with acetic acid over MnO at 400-410°C.

Ketones V were also obtained via the scheme



V, VII–IX a $R=C_4H_9$; b $R=C_5H_{11}$; c $R=H$

Scientific-Research Institute of Organic Intermediates and Dyes, Moscow 103787. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 5, pp. 643-647, May, 1984. Original article submitted August 23, 1983.

TABLE 1. Characteristics of the Synthesized Compounds

Compound	bp, °C (hPa)	n_D^{20}	Found, %			Empirical formula	Calc., %			Yield, %
			C	H	N		C	H	N	
Ia	103—105 (1)	1,5185	82,5	10,1	7,4	$C_{13}H_{19}N$	82,4	10,2	7,3	46, 26[a]
Ib	148—150 (8)	1,5180	82,9	10,4	7,1	$C_{14}H_{21}N$	82,7	10,4	6,9	20[a]
Ic	155—156 (2)	1,5075	83,1	11,2	6,0	$C_{17}H_{27}N$	83,2	11,1	5,7	16[a]
Id	174—176 (2)	1,5060	83,4	11,7	5,0	$C_{20}H_{33}N$	83,6	11,6	4,9	10[a]
trans -IIa	82—84 (3)	1,4676	—	—	—	$C_{13}H_{22}O$	—	—	—	85[b]
cis-IIa	80—83 (1)	1,4680	—	—	—	$C_{13}H_{22}O$	—	—	—	86[b]
IVa	133—135 (1)	1,4971	77,9	11,3	5,0	$C_{18}H_{31}NO$	78,0	11,0	5,0	75
trans -Va	128—129 (20)	1,4588	79,2	12,3	—	$C_{12}N_{22}O$	79,1	12,2	—	46
trans-Vb	151—153 (19)	1,4600	79,8	12,6	—	$C_{14}H_{26}O$	79,9	12,5	—	45
cis-Va	127—129 (19)	1,4604	79,3	12,2	—	$C_{12}H_{22}O$	79,1	12,2	—	96
cis-Vb	136—138 (16)	1,4611	79,7	12,4	—	$C_{13}H_{24}O$	79,5	12,3	—	97
VIIIa	85—87 (2)	—	79,8	11,5	—	$C_{12}H_{20}O$	79,9	11,2	—	72
VIIIb	92—93 (2)	—	80,4	11,3	—	$C_{13}H_{22}O$	80,4	11,4	—	77
IXa	135—137 (15)	1,4806	79,8	11,3	—	$C_{12}H_{20}O$	79,9	11,2	—	91
IXb	147—149 (15)	1,4811	80,4	11,5	—	$C_{13}H_{22}O$	80,4	11,4	—	87

[a] Based on ketone V.
[b] Contains ~10% admixed ketone Va, according to data from the PMR spectrum.

Alcohols VIIIa,b,c were synthesized in 72-77% yields from the 4-n-alkylcyclohexanones described in [6] in diglyme in the presence of powdered potassium hydroxide by a method similar to that in [7]. Ethynylation of ketones VIIa-c in liquid ammonia gives VIII in low yields (15-20%). It has been reported [8] that treatment of alcohol VIIIc with formic acid with subsequent hydrogenation over Ni/Re leads to cyclohexylacetaldehyde. In addition, the formation of unsaturated ketones or mixtures of the latter with unsaturated aldehydes when ethynylcarbinols are heated with acids has been described [9, 10].

We have shown that under the conditions in [8] alcohols VIII form only ketones IX in ~90% yields, the hydrogenation of which over Ni/Re leads to mixtures consisting of 80% cis-ketone V and 20% trans-ketone V, according to data from the PMR spectra.

The PMR spectra of isomeric cis- and trans-ketones V differ little; however, it was established by means of $Eu(FOD)_3$ [tris(1,1,1,2,2,3,3-heptafluoro-7,7-dimethyl-3,5-octanedionato)europium] that the signal of the protons of the acetyl group of trans isomers V is shifted to weaker field (see Table 2). In addition, cis isomers V have higher refractive indexes (n_D^{20}) (see Table 1).

The condensation of trans-vinyl ketones II with enamines III takes place at 20°C and leads to the formation of pyran derivatives IVa-d in 50-75% yields. Treatment of the latter with hydroxylamine hydrochloride leads to pyridines Ia-d in 40-50% yields.

The PMR spectra of the products of the reaction of enamines IIIa,b with the cis isomer of vinyl ketones II do not contain the signal of a vinyl proton at 5.2 ppm that is characteristic for IV; in addition, they are not converted to pyridine derivatives under the influence of hydroxylamine hydrochloride. These facts constitute evidence that the cis isomers of vinyl ketones II do not undergo diene condensation with enamines III.

The trans isomers of vinyl ketones II evidently contain both substituents in equatorial orientations of the cyclohexane ring. The cis isomers of II should contain an acrylyl group (which, like other acyl groups, has a lower conformational energy than alkyl substituents [11]) in a sterically more hindered (axial) position of the ring. For steric reasons, it probably cannot assume a cisoid conformation and cannot undergo a reaction of the diene synthesis type with enamines. The lower λ_{max} and log ε values of the bands of the UV spectra and the higher frequencies of the most intense bands of stretching vibrations of the carbonyl group in the IR spectra as compared with the bands for the trans isomers of II indicate the lower degree of conjugation of the ethylene and carbonyl double bonds in the acrylyl group of the cis isomers of II and, consequently, disruption of its planar structure.

The structures of Ia-d were confirmed by the results of elementary analysis and data from the PMR and UV spectra. Let us note that, according to our data, the synthesis of similar compounds through organolithium derivatives of pyridine leads to mixtures of cis and trans isomers of I. According to the ^{13}C NMR spectra, the chemical shifts of the signals of the analogous carbon atoms in the cis and trans conformations differ. The presence of

TABLE 2. Spectra Data for the Compounds Obtained

Compound	UV spectrum, λ_{max}, nm (log ε)	IR spectrum, νC=O, cm^{-1}	PMR spectrum, δ, ppm
Ia	214 (3,88), 269 (3,56)	—	1,16 (t, CH$_3$)[a]; 1,3—2,0 [m (CH$_2$)$_n$]; 2,5 (m, CHAr); 2,55 (q, CH$_2$Ar)[a]; 6,92 (d, 3-H)[b], 7,26 (dd., 4-H)[c]; 8,24 (d, 6-H)[d]
Ib	214 (3,81), 270 (3,53)	—	0,88 (t CH$_3$)[a]; 1,1—1,9 [m, (CH$_2$)$_n$]; 2,44 (т, CH$_2$Ar)[a]; 2,5 (m, CHAr); 6,88 (d, 3-H)[b]; 7,24 (dd, 4-H)[c]; 8,19 (d, 6-H)[d]
Ic	214 (3,72), 269 (3,39)	—	0,85 (t, CH$_3$)[a]; 1,18 (t, CH$_3$)[a]; 1,1—2,0 [m (CH$_2$)$_n$. CH]; 2,5 (m CHAr); 2,55 (q, CH$_2$Ar)[a]; 6,89 (d, 3-H)[b], 7,26 (dd, 4-H)[c]; 8,21 (d, 6-H)[d]
Id	215 (3,94), 271 (3,62)	—	0,86 (t, CH$_3$)[a]; 0,88 (t, CH$_3$)[a]; 1,1—2,0 [m (CH$_2$)$_n$, CH]; 2,48 (t, CH$_2$Ar)[a]; 2,5 (m CHAr); 6,93 (d, 3-H)[b], 7,28 (dd, 4-H)[c]; 8,25 (d, 6-H)[d]
trans-IIa	214 (3,75), 266 (3,27), 337 (2,49)	1700 m., 1687 in., 1665 w.	0,83 (t, CH$_3$)[a]; 1,0—1,5 [m, (CH$_2$)$_n$]; 1,7—1,9 (m, CH$_2$CCO); 2,3—2,6 (m, CHCO); 5,61 (dd, CH=C)[e]; 6,2—6,4 (m, CH$_2$=C)
cis-IIa	213 (3,17), 261 (2,04), 333 (1,66)	1700 in., 1690 m., 1665 w.	0,81 (t, CH$_3$)[a]; 1,0—1,5 [m, (CH$_2$)$_n$]; 1,7—1,9 (m, CH$_2$CCO); 2,3—2,6 (m CHCO); 5,59 (dd, CH=C)[e]; 6,1—6,3 (m CH$_2$=C)
IVa	220 (3,61)	—	0,91 (t, CH$_3$)[a]; 1,1—2,9 [m (CH$_2$)$_n$, (CH)$_2$]; 5,19 (m, CH=C)
trans-Va	—	1720	0,87 (t, CH$_3$)[a]; 1,23 [m (CH$_2$)$_n$]; 1,7—1,9 (m, CH); 2,02 (s, CH$_3$CO); 2,3 (m, CHCO)
trans-Vb	—	1720	0,88 (t, CH$_3$)[a]; 1,22 [m (CH$_2$)$_n$]; 1,7—1,9 (m, CH); 2,01 (s, CH$_3$CO); 2,3 (m, CHCO)
cis-Va	—	1720	0,88 (t, CH$_3$)[a]; 1,23 [m (CH$_2$)$_n$]; 1,7—1,9 (m, CH); 2,03 (s, CH$_3$CO); 2,3 (m CHCO)
cis-Vb	—	1710	0,88 (t, CH$_3$)[a]; 1,23 [m, (CH$_2$)$_n$]; 1,7—1,9 (m, CH); 2,0 (s, CH$_3$CO); 2,3 (m, CHCO)
IXa	233 (2,72), 307 (1,67)	1680	0,88 (t, CH$_3$)[a]; 1,25 [m (CH$_2$)$_n$]; 2,10 (s, CH$_3$CO); 1,5—2,5 (m CH, CH$_2$C=C); 6,75 (m, CH=C)
IXb	236 (3,07), 307 (1,69)	1675	0,81 (t, CH$_3$)[a]; 1,20 [m (CH$_2$)$_n$]; 2,00 (s, CH$_3$CO); 1,5—2,5 (m, CH, CH$_2$C=C); 6,65 (m, CH=C)

[a] J = 5-6 Hz.
[b] J = 8-9 Hz.
[c] J = 2 and 8-9 Hz.
[d] J = 2 Hz.
[e] J = 4 and 9-10 Hz.

only some signals of the carbon atoms in the spectra of I obtained by the method indicated above constitutes evidence for the presence of only one conformation. On the basis of the fact that only the trans isomers of vinyl ketones II undergo the reaction, it may be assumed that I are only trans isomers. The establishment of the precise structures of I will be the subject of our future communications.

EXPERIMENTAL

The UV spectra of solutions of the compounds in ethanol were recorded with a Specord UV-vis spectrophotometer. The IR spectra of thin layers of the compounds were recorded with a UR-20 spectrometer. The PMR spectra of soluctions in CCl$_4$ were obtained with a Tesla BS-487C spectrometer (80 MHz) with hexamethyldisiloxane as the internal standard. The characteristics of the compounds synthesized for the first time are presented in Tables 1 and 2.

trans-1-n-Alkyl-4-acetylcyclohexanes (Va-c). A 30-ml sample of methanol was passed at 400-410°C at a rate of 15 drops/min through a tube made of high-melting glass with a diameter of 2 cm and a length of 40 cm filled with an MnO catalyst [12], after which a solution of 0.1 mole of 4-n-alkyl-trans-cyclohexanecarboxylic acid VI in 86 ml (1.5 mole) of acetic acid was passed through the tube. The acetone was separated from the catalyst by distillation, and the residue was extracted with ether (two 50-ml portions). The extract was dried with Na$_2$SO$_4$ and distilled.

4-n-Alkyl-1-ethynyl-1-cyclohexanols (VIIIa-c). A fast stream of acetylene (previously passed through two wash bottles containing concentrated sulfuric acid to remove traces of acetone) was passed with vigorous stirring at −10°C for 2 h into a suspension of 156.8 g (2.8 moles) of powdered potassium hydroxide in 300 ml of absolute diglyme, after which, without interrupting the flow of acetylene, a solution of 0.5 mole of 4-n-alkylcyclohexanone VIIa-c in 130 ml of diglyme was added dropwise in the course of an hour. The reaction mixture was maintained at −15°C in a stream of acetylene for 4 h and allowed to stand at room temperature for 12 h. It was then decomposed with 400 ml of water, 50 ml of acetic acid was added, and the mixture was extracted with ether (two 150-ml portions). The combined ether extracts were washed with a saturated solution of sodium chloride, dried with Na_2SO_4, and distilled over a small amount (∿0.2 g) of succinic acid.

4-n-Alkyl-1-acetyl-1-cyclohexenes (IXa-c). A mixture of 0.15 mole of alcohol VIIIa-c and 240 ml of 86% HCOOH was refluxed for 2.5 h, after which the HCOOH was removed by distillation *in vacuo*, and the residue was dissolved in 100 ml of ether. The solution was washed with a solution of sodium carbonate to pH 8-9 and with water, dried over Na_2SO_4, and distilled.

cis-1-n-Alkyl-4-acetylcyclohexanes (Va,b). An 8-g sample of a Raney nickel catalyst was added to a solution of 0.05 mole of IXa,b in 150 ml of ethanol and hydrogenated at 20°C until 0.05 mole of hydrogen had been absorbed. The catalyst was removed by filtration, and the filtrate was distilled.

trans- and cis-1-Acrylyl-4-n-alkylcyclohexanes (IIa-c). A mixture of 0.1 mole of ketone V, 10.8 g (0.12 mole) of paraformaldehyde (trioxymethylene), 22.1 g (0.1 mole) of N-methylaniline trifluoroacetate (obtained by mixing equimolar amounts of trifluoroacetic acid and N-methylaniline in benzene at 10°C), and 120 ml of anhydrous tetrahydrofuran (THF) was refluxed for 5 h in a nitrogen atmosphere, after which a solution of 5.4 g (0.06 mole) of trioxymethylene and 11 g (0.05 mole) of N-methylaniline trifluoroacetate in 60 ml of THF was added, and the mixture was refluxed for 5 h. It was then diluted with 200 ml of pentane at 20°C, and the mixture was washed with water and $NaHCO_3$ solution and dried with Na_2SO_4. The solvent was removed by vacuum distillation, and the residue was passed through a thin layer of silica gel and used rapidly in the next step without distillation. Compound IIa was distilled in a stream of nitrogen. The constants are presented in Tables 1 and 2.

3-n-Alkyl-6-(trans-4-n-alkylcyclohexyl)-3,4-dihydro-2-N-piperidino-2H-pyrans (IVa-d). A mixture of 0.09 mole of trans-vinyl ketone IIa-c and 0.08 mole of the enamine was maintained at 20°C for 80 h, after which the residual starting substances (Ia-c and IIIa,b) were removed by vacuum distillation. To avoid decomposition, IVb-d were not distilled but were used without purification in the next step. Compounds IVa, IVb, IVc, and IVd were obtained in 70%, 73%, 55%, and 60% yields, respectively.

5-n-Alkyl-2-(trans-4-n-alkylcyclohexyl)pyridines (Ia-d). A mixture of 30 ml of water, 30 ml of ethanol, 25.5 g (0.37 mole) of hydroxylamine hydrochloride, and 0.12 mole of IVa-d was refluxed for 2 h, after which the ethanol was removed by distillation, and the residue was shaken with a mixture of 5% HCl and ether. In the case of Ia the aqueous layer was made alkaline to pH 9 with NaOH and extracted with ether (two 50-ml portions), whereas in the case of Ib-d the ether layer was washed with Na_2CO_3 solution. The ether extract was dried over Na_2SO_4 and distilled.

LITERATURE CITED

1. M. Carissime, Farm. Ed. Sci., 34, 1039 (1979).
2. C. Botteghi, G. Caccia, and S. Gladiali, Synth. Commun., 9, 69 (1979).
3. R. Dulou, E. Elkik, and A. Veillard, Bull. Soc. Chim. Fr., No. 5, 967 (1960).
4. J.-L. Gras, Tetrahedron Lett., No. 32, 2955 (1978).
5. H. Schubert, V. Uhlig, and R. Dehne, Z. Chem., 12, 219 (1972).
6. W. Sucrow and H. Wolter, Chimia, 36, 460 (1982).
7. R. Kh. Geivandov and E. I. Kovshev, Zh. Org. Khim., 15, 218 (1979).
8. H. Rupe, W. Messner, and E. Kambli, Helv. Chim. Acta, 11, 449 (1928).
9. M. Kagawa, Chem. Pharm. Bull. (Tokyo), 9, 391 (1961); Chem. Abstr., 55, 24808 (1961).
10. F. G. Fischer and K. Lowenberg, Ann. Chem., 475, 183 (1929).
11. A. Gordon and R. Ford, The Chemist's Companion, Wiley (1973).
12. V. M. Potapov and A. P. Terent'ev, Zh. Obshch. Khim., 28, 3323 (1958).