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Abstract

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SYNTHESIS OF CYCLOALKANO-2,3-PYRROLIDINES AND THE STERIC DIRECTION OF THE LEUCKART REACTION

The synthesis of cycloalkano-2,3-pyrrolidines, especially perhydroindoles and their closest homologs—cyclopentano-2,3-pyrrolidines—is of considerable interest. In undertaking the synthesis of compounds of this type, we took as a basis the method previously developed by us for obtaining pyrrolidine bases by hydroamination (the Leuckart reaction) of γ-keto alcohols (*1*). The interaction of the corresponding monocyclic keto alcohols or keto halides (I–IV) with formamide and its N-substituted derivatives should have led to the corresponding cycloalkano-2,3-pyrrolidines

[structural scheme]

$n = 1$, I $X = OH$,
II $X = Cl$,
III $X = Br$,
$n = 2$, IV $X = Cl$;

$n = 1$, V–IX, $R = -H$, $-CH_3$, $-C_2H_5$, $-n\text{-}C_4H_9$, $-CH_2C_6H_5$;
$n = 2$, X–XIV, $R = -H$, $-CH_3$, $-C_2H_5$, $-n\text{-}C_4H_9$, $-CH_2C_6H_5$;

The keto alcohol and keto halides required for this purpose (I–III) were obtained by methods described in the literature (*2, 3*). 2-(β-Chloroethyl)-cyclohexanone (IV) was synthesized from 2-ketocyclohexylacetic ester by reduction of its ethylene ketal with lithium aluminum hydride (*4*), followed by hydrolysis of the resulting ketal of the keto alcohol with hydrochloric acid. The conversion of compounds (I–IV) (compounds of type A) under the conditions of the Leuckart reaction, in all probability, proceeds through the following stages:

$$(A) \xrightarrow{HCONHR} (B) \xrightarrow{H^+} (C) \xrightarrow{OH^-} (D)$$

On the first stage (the Leuckart reaction proper), reductive amination of the keto group in a compound of type A by formamide or its N-substituted derivative takes place, leading to the formation of formylated amines of type B. The latter,

upon acid hydrolysis, readily split off the formyl group; under these conditions the possibility is not excluded of replacement of one group X by X′; for example, upon hydrolysis of a chloride or bromide the corresponding alcohol may be formed. The amino alcohol or amino halide (C) thus formed then undergoes intramolecular cyclization with formation of cyclo-

cycloalkano-2,3-pyrrolidines (compounds of type D). Indeed, in the reaction of 2-(β-bromoethyl)cyclopentanone (III) with formamide and its N-substituted derivatives, cyclopentano-2,3-pyrrolidines (V–IV)* were obtained in good yields. Similarly, from 2-(β-chloroethyl)cyclohexanone (IV), the corresponding cyclohexano-2,3-pyrrolidines (perhydroindoles) (X–XIV) are formed in yields reaching 60%. Thus, we have established that γ-keto alcohols and γ-keto halides can serve as starting materials in the preparative synthesis of cycloalkano-2,3-pyrrolidines (see Table 1). The elemental-analysis data for all the compounds obtained are in good agreement with the theoretically calculated values.

Table 1

Cycloalkano-2,3-pyrrolidines

structure: fused cycloalkane–pyrrolidine system $(H_2C)_n$, $N-R$

n	R	B.p., °C/mm Hg	Empirical formula	n_D^{20}	d_4^{20}	MR_D	Yield, %
1	H	60–61/10	$C_7H_{13}N$	1.4868	0.9473	33.65 (33.72)*	20
1	CH_3	70–71/12	$C_8H_{15}N$	1.4682	0.9055	38.46 (38.68)	20
1	C_2H_5	95–96/10	$C_9H_{17}N$	1.4655	0.8995	42.81 (43.3)	21
1	*n*-C_4H_9	70–72/12	$C_{11}H_{21}N$	1.4720	0.892	53.58 (52.83)	42.7
1	$CH_2C_6H_5$	156–157/10	$C_{14}H_{19}N$	1.5339	0.985	63.45 (63.26)	60
2	H	80–81/20	$C_8H_{15}N$	1.4879	0.947	38.10 (38.34)	20
2	CH_3	50–52/10	$C_9H_{17}N$	1.4712	0.9026	43.1 (43.5)	36
2	C_2H_5	70–72/14	$C_{10}H_{19}N$	1.4759	0.8989	47.90 (47.92)	30
2	*n*-C_4H_9	97–99/7	$C_{14}H_{23}N$	1.4720	0.8920	56.52 (57.15)	52
2	$CH_2C_6H_5$	158–160/10	$C_{15}H_{21}N$	1.5372	0.9938	67.92 (67.4)	60

* Calculated values are given in parentheses.

All the cycloalkano-2,3-pyrrolidines obtained were chromatographed in a thin layer of aluminum oxide; this revealed the presence of a mixture of isomeric compounds:

cis form trans form

The data available in the literature note the steric direction of the hydroamination reaction (Leuckart reaction) of certain alkyl-substituted carbonyl compounds, with preferential formation of cis-alkylamines ([3],[6]).

* A preliminary communication on this synthesis was published by us in 1962 ([5]).

Preparative separation of the isomeric cycloalkano-2,3-pyrrolidines obtained by us on an alumina plate in the benzene : acetone system (in various ratios) made it possible to quantitatively assess the ratio of the cis- and trans-isomers. In the case of cyclopentano-2,3-pyrrolidine and its N-substituted derivatives, a predominant tendency toward formation of the trans-form was observed. For cyclohexano-2,3-pyrrolidines, formation of the cis-form of the pyrrolidines proved preferable. The melting points of certain derivatives of the pyrrolidine bases corresponding to the cis- and trans-forms agree well with the available literature data ([3,7–10]).

The quantitative ratio of the cis- and trans-forms of the amines obtained is given in Table 2.

Table 2

Results of preparative separation on alumina

cycloalkano-2,3-pyrrolidine skeleton
$(H_2C)_n$, N—R

n	R	Cis-form, m.p., °C	Trans-form, m.p., °C	R_f of cis-trans forms	Solvent system	Ratio of cis-trans forms, %
1	H	——	picrate 87–88° (87–90° ([3,7]))*picrolonate 239, 240° (239° ([3,7])) 3,5-dinitrobenzoate 157–158° (157° ([3,7]))	0,63	$CHCl_3$ (sat. NH_3 at 20°) — C_2H_5OH = 30 : 2	100
1	CH_3	picrate 220° (219–220° ([3,7])) picrolonate 206–207° (207° ([3,7]))	picrate 196–197° (196° ([3])) picrolonate 182° (182° ([3]))	0,54/0,28	C_6H_6 : $(CH_3)_2CO$ = 6 : 1	82/18
2	H	picrate 137–138° (137° ([10])) picrolonate 219–220° (218° ([10]))	——	0,46	$CHCl_3$ (sat. NH_3 at 20°)	100
2	CH_3	picrate 203–205° (204° ([10])) picrolonate 167–168° (168° ([10]))	picrate 195–196° (196° ([10])) picrolonate 181–182° (182° ([10]))	0,51/0,29	C_6H_6 : $(CH_3)_2CO$ = 5 : 1	90/10

* Literature data are given in parentheses.

Experimental Part

2-(β-Bromoethyl)cyclopentanone was prepared by the method of Mayer ([2]) and King ([3]). Yield 28%. B.p. 130–135°/2 mm, $n_D^{22} = 1.4802$, $d_4^{22} = 1.2911$. Literature data: b.p. 143–144°/4 mm ([2]).

2-(β-Chloroethyl)cyclohexanone (IV). The ketal of 2-(β-hydroxyethyl)cyclohexanone

was obtained from 2-ketocyclohexylacetic ester by reduction of its ethylene ketal with lithium aluminum hydride ([4]). Then 20 g (0.1 mol) of the ethylene ketal of the keto alcohol was mixed with 60 ml of conc. hydrochloric acid and boiled for 1 h. The reaction mixture was neutralized with solid potassium carbonate and extracted with benzene. After removal of the solvent, the residue was purified on an alumina column in the $C_6H_6 : CHCl_3 = 17 : 3$ system. 15.5 g (97%) of IV was obtained, $n_D^{18} = 1.4890$.

Cycloalkano-2,3-pyrrolidines. The procedure for preparing cycloalkano-2,3-pyrrolidines from the corresponding I–IV is analogous to the procedure for the synthesis of cyclopentano-2,3-pyrrolidines reported by us in 1962 ([5]).

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Note: Figure translations are in progress. See original paper for figures.