SYNTHESIS AND STEREOCHEMISTRY OF 1-SUBSTITUTED--10-HYDROXYDECAHYDROISOQUINOLINES

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The simple synthesis of 1-substituted-10-hydroxydecahydroisoquinolines *via* Prins-like proton-catalyzed reactions of 2-(cyclohex-1-enyl)ethylamine with aliphatic, aromatic and hetero-aromatic aldehydes is described. All reactions yielded only one stereoisomeric (racemic) compound, as proved by proton magnetic resonance experiments.

After GREWE's publication of the first synthesis and anaesthetic action of *N*-methylmorphinane (I), one of the starting materials of morphine synthesis [1, 2], great efforts were made to produce rational synthones for morphinane derivatives (Fig. 1). The first syntheses of 1-substituted-10-hydroxydecahydroisoquinolines were published by GREWE [3] and HENECKA [4].

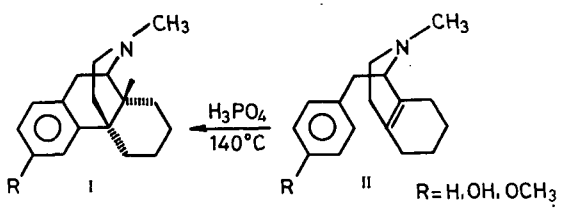


Fig. 1.

The simplest 10-hydroxydecahydroisoquinoline (IV) was made in high yield by the proton-catalyzed reaction of 2-(cyclohex-1-enyl)ethylamine (III) and formaldehyde (Fig. 2). The 1-benzyl and 1-*p*-methoxy-benzyl derivatives could be produced in low or moderate yields, depending upon the rate of self-condensation of the aldehyde.

GREWE and coworkers [3] investigated the transformation of 10-hydroxydeca-hydroisoquinoline to 1,2,3,4,5,6,7,8-octahydroisoquinoline. They found that the proton-catalyzed elimination of 10-hydroxydeca-hydroisoquinoline yielded three products; the

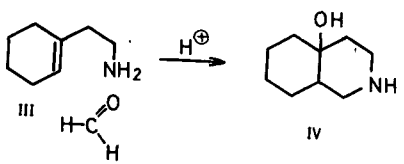


Fig. 2.

desired compound with double bond involved in the annelation could be produced only from the corresponding 10-chloro derivatives by elimination of the halogen with methanolic potassium hydroxide.

These observations led to the conclusion of the *cis*-annelation of the rings, and this was proved by the pmr data of GROB and WOHL [5, 6]. These authors synthetized Grewe's compound and isomerized it to the corresponding *trans*-derivative. They assigned the stereoisomers on the basis of the temperature-dependence of the pmr signals. Grewe's compound (V, VI) was found to be the *cis*-isomer because of its conformational equilibrium. The absence of thermal equilibrium of the isomerized product (VII) showed that the compound was the *trans*-isomer (see Fig. 3).

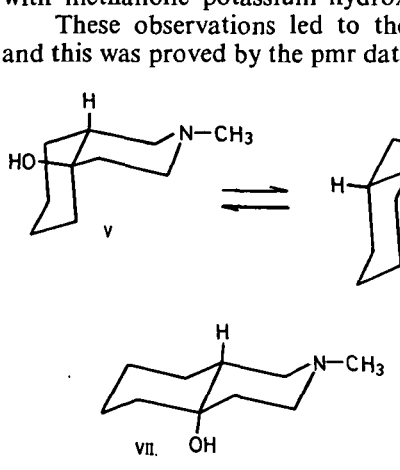
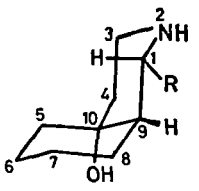


Fig. 3.

Since further 1-substituted-10-hydroxydecahydroisoquinolines have not been described in the literature, we have attempted to find a rational synthesis of these compounds and to investigate the steric structure of the 1-substitution.

2-(Cyclohex-1-enyl)ethylamine was synthetized by modifying [8, 9] the method of SCHNIDER and HELLERBACH [7]. (Cyclohex-1-enyl)acetonitrile was reduced in ammoniacal ethanolic solution with Raney Ni catalyst. After equivalent hydrogen absorption, the reaction mixture contained not only the desired 2-(cyclohex-1-enyl)ethylamine, but also 15—20% 2-cyclohexylethylamine and 3—5% secondary amines. Cyclohexenylethylamine and cyclohexylethylamine could not be separated by distillation, and therefore the reaction was stopped at an optimum position (70% hydrogen absorption). In this mixture only the nitrile and the cyclohexenylethylamine were present [9] and the amine could be separated simply by acidic extraction.

The cyclization reaction was carried out on the amine hydrochloride dissolved in water or in 60% aqueous ethanol. The solution was adjusted to pH=2—6 by hydrochloric acid addition and the aldehyde was then added. The aliphatic aldehydes were reacted for 6—16 h at room temperature, whereas for the aromatic aldehydes the reaction mixture was boiled for 20—24 h. The 10-hydroxydecahydroisoquinolines were produced in 75—90% yields (Fig. 4).



VIII R = methyl
IX R = furyl
X R = phenyl
XI R = p-nitro-phenyl
XII R = p-chloro-phenyl
XIII R = p-methoxy-phenyl
XIV R = p-ethoxy-phenyl
XV R = p-methoxy-benzyl

Fig. 4.

1-(*p*-Methoxybenzyl)-10-hydroxydecahydroisoquinoline was prepared after HENECKA [4], this method being modified in that the *p*-methoxyphenylglycidic acid methyl ester in toluene solution was added to the solution of 2-(cyclohex-1-enyl)ethylamine hydrochloride. In this way, the yields were increased to 54%. The stereoisomerism of the prepared 1-substituted-10-hydroxydecahydroisoquinolines was investigated by pmr spectroscopy. These compounds are stereochemically more complicated systems than compound (IV). In this case therefore Grob's method for the evaluation of the ring annelation could not be applied, because the 1-substituents caused rigidity of the *cis*-2-azadecaline.

The ring annelation was determined by pmr *via* trichloroacetyl-isocyanate (TAI) shift values of selected protons of the compounds. TAI reacted slowly with the protons of hydroxy groups, but quickly with the amine-groups of the compounds, and therefore the values of $J_{H1,H9}$ could be determined from the spectra of the corresponding urethane derivatives (Table I). These values lie in the range 10—11 Hz,

Table I

Trichloroacetyl-isocyanate shifts of C_1 *protons*

Compound	$\delta(H^1)$ (ppm)	$\delta(H^1)$+TAI (ppm)	$\Delta\delta(H_1)$ (ppm)	$J_{1,9}$ (Hz)
IV	2.85	3.70	0.85	10
VIII	2.8	4.30	1.50	10.5
IX	4.05	5.30	1.25	11
X	3.75	5.35	1.60	10.5
XI	3.90	5.45	1.55	10
XII	3.80	5.25	1.55	10.5
XIII	3.65	5.25	1.60	10
XIV	3.70	5.30	1.60	10.5
XV	2.80	4.35	1.55	10

and therefore H_1 and H_9 are situated at a dihedral angle of about 180°; hence, the arrangement of the carbon-hydrogen bonds is *trans*-diaxial. In the original (not shifted) spectra the H_9 signals occur at frequencies where the signals of the bulk aliphatic hydrogens are present, and the accurate values of the shifts can therefore not be determined exactly.

The estimated approximate values of the shifts are 1.1—1.2 ppm. This large TAI shift value of the H_9 signal means that the hydroxy group and H_9 are in close proximity to each other *i.e.* they are in the *syn*-position and therefore the ring-annelation must be *cis*.

On this basis it was concluded that the 1-substituted-decahydroisoquinolines contain a *cis*-2-azadecalin skeleton in which the 10-hydroxy group is axial to the cyclohexane ring, and the 1-substituent is equatorial to the piperidine ring. The

sharpness of the signals of the ring protons may suggest the restricted conformational mobilities of the compounds investigated.

The suggested spatial arrangement of the compounds also indicated that the reaction is not of Mannich type, as specified previously by GROB [4], but is of Prins type, the original olefin reacting via *trans*-diaxial addition (Fig. 5). In this way one may rationalize the absence of the other *cis*-isomer (the hydroxy group equatorial to the cyclohexane ring, and the 1-substituent equatorial to the pireridine ring), for in this transitional state of *trans*-diaxial addition the other enantiotopic face of the azomethine should react; this produces overcrowding between the 1-substituent and the cyclohexenyl part of the molecule, and accordingly this transition state may be excluded.

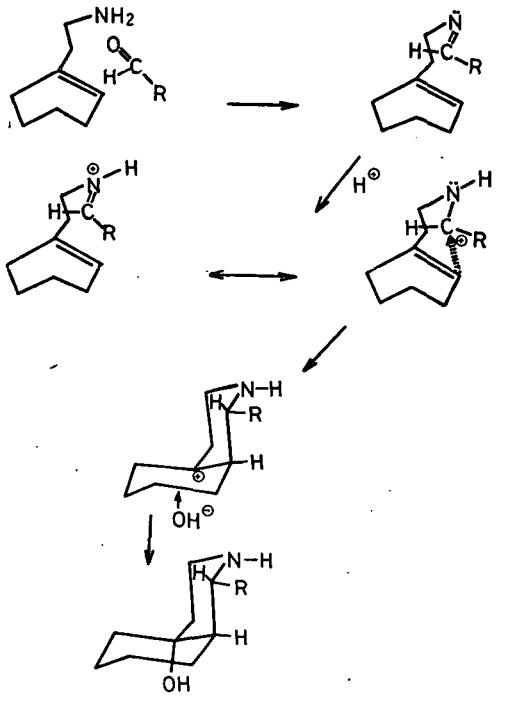


Fig. 5.

Experimental

Melting points were determined on a PHMK (Dreden) hot stage, and were not corrected. The pmr spectra (see the data in Table II) were measured in Merck Uvasol $CDCl_3$ solution relative to TMS with a JEOL 60 HL spectrometer. The IR spectra were recorded in KBr pellets with a UNICAM SP 1000 spectrometer.

The TLC plates was made from Kieselgel G (REANAL, Budapest), or Silufol UV (Kavalier, Czechoslovakia) precoated plates were used. The potentiometric titrations were performed with a Mettler potentiograph. The GLC separations were carried out on a Carlo Erba Fractovap chromatograph.

10-Hydroxydecahydroisoquinoline (IV)

125.2 g 2-(cyclohexen-1-yl)ethylamine was dissolved in 1000 ml 1 N HCl, and the solution was adjusted to pH=2 by further conc. HCl addition. With stirring for about 2 h, 74 ml 38% aqueous formaldehyde solution was added at 35—40 °C, and with continuous stirring the mixture was held at the same temperature for a further 6 h. The reaction mixture was then evaporated to dryness from a bath at 40 °C. The residue, crystallized from a methanol—acetone mixture, yielded 172 g 10-hydroxydecahydroisoquinoline hydrochloride, mp: 248—50 °C (decomp.).
Anal.: $C_9H_{17}NO.HCl$; M.W.: 191.702; calcd. $Cl^- = 18.49$; found $Cl^- = 18.40\%$.
10 g 10-hydroxydecahydroisoquinoline hydrochloride was dissolved in 25 ml water,

Table II

The pmr data on 1-substituted-10-hydroxydecahydroisoquinolines

Compound	$\delta(H_1)$	$\delta H)$	$\delta(OH)$	$\delta(H_9)$	$\delta(H_3)$	Other characteristic signals
IV	2.65; 3.1 (2H)	1.6	1.6	2.72	2.95; 3.05 (2H)	
IV	2.9 (1H)	1.6	1.6	—	2.95; 3.05 (2H)	1.1 (CH_3)
IX	4.05 (1H)	1.7	1.7	—	2.90; 3.05 (2H)	6.25; 7.2; 7.3; (3H, furyl)
X	3.75 (1H)	1.6	1.6	—	2.95; 3.05 (2H)	7.21 (s, 5H, aromatic)
XI	3.90 (1H)	1.6	1.6		2.95; 3.05 (2H)	7.45; 8.15 (4H, aromatic)
XII	3.80 (1H)	1.55	1.55	—	2.95; 3.05 (2H)	7.3 (s, 4H, aromatic)
XIII	3.65 (1H)	1.65	1.65	—	2.90; 3.05 (2H)	3.75 (s, 3H, OCH_3) 6.85; 7.35 (4H, arom.)
XIV	3.70 (1H)	1.7	1.7	—	2.90; 3.05 (2H)	1.42; 4.00 (5H—OCH_2—CH_3) 6.85; 7.30 (4H, aromatic)
XV	2.8 (1H)	1.6	1.6	—	2.90; 3.05 (2H)	2.48 (dd, 1H) 3.08 (dd, 1H)

and 50 ml of a benzene—1-butanol (7:3) mixture was added to the solution. With stirring, 4 ml 40% aqueous NaOH solution was added gradually to yield pH=12. The organic layer was then separated, and the aqueous part was extracted with 2×50 ml benzene—1-butanol (7:3) mixture. The extracts were combined dried over KOH pellets and evaporated to dryness *in vacuo*. The residue, crystallized from benzene, yielded 7.3 g (90%) 10-hydroxydecahydroisoquinoline. After four crystallizations and sublimations, the mp of the compound was 119—119.5 °C (the literature [4] gave 117 °C)

Anal.: $C_9H_{17}NO$; M.W.: 155.241; (M.W. measured potentiometrically: 155)

Calcd:	C=69.63	found:	C=69.47
	H=11.04		H=10.92
	N= 9.02		N= 8.83

1-Methyl-10-hydroxydecahydroisoquinoline (VIII)

12.52 g (0.1 mole) 2-(cyclohex-1-enyl)ethylamine was dissolved in 100 ml 1 N HCl and the solution was adjusted to pH=2 with conc. HCl. With stirring for about 1 h at 35—40 °C, 50 ml aqueous solution of 4.84 g (0.11 mole) acetaldehyde was added gradually and stirring was continued for a further 16 h. The reaction mixture was then evaporated to dryness on a 50 °C bath. The residue, crystallized twice from methanol—acetone, yielded the hydrochloride salt of the isoquinoline: 15.6 g, mp: 262—264 °C (decomp.).

Anal: $C_{10}H_{19}NO$; M.W.: 205.729; calcd. Cl^-=17.23; found Cl^-=17.18%.

The corresponding amine base was prepared as described above. After crystallization from benzene, the mp was 174—175 °C.

Anal: $C_{10}H_{17}NO$; M.W.: 169.268; (M.W. measured potentiometrically: 170).

Calcd.:	C=70.96	found:	C=71.24
	H=11.31		H=11.60
	N= 8.28		N= 8.44

1-(p-Methoxybenzyl)-10-hydroxydecahydroisoquinoline (XIV)

The reaction described previously by HENECKA [4] and SOKHOLOWA [8] was modified to give higher yields.

125.2 g (1 mole) 2-(cyclohex-1-enyl)ethylamine and 192.2 g (1 mole) *p*-methoxypenylglycidic acid methyl ester were dissolved in 300 mol toluene and emulsified in 3000 ml water with intensive stirring. The stirring was continued and the emulsion was acidified to pH=3.4—3.6 with conc. HCl. The acidic emulsion was boiled with continous stirring for 48 h. The aqueous phase was then separated and the organic layer extracted three times with 100 ml 4 N HCl. The aqueous extracts were combined, mixed with small amounts of decolourizing carbon and filtered. 100 ml benzene was added to the solution, which was then made alkaline (pH=12) with 40% aqueous NaOH solution. The benzene layer was separated, and dried over sodium sulphate. On cooling 1-(*p*-methoxybenzyl)-10-hydroxydecahydroisoquinoline crystallized. The colourless crystals were filtered off, washed with a small amount of benzene and dried. Yield: 129.4 g, mp: 151 °C. Distillation of the mother liquor

at reduced pressure yielded 23 g 2-(cyclohex-1-enyl)ethylamine (bp_{12} 77 °C). Evaporation of the residue and crystallization from methanol yielded a further 13.8 g 1-(*p*-methoxybenzyl)-10-hydroxydecahydroisoquinoline (mp: 150—151 °C). The analytical sample crystallized from methanol had mp: 152 °C.

Anal.: $C_{17}H_{24}NO_2$; M.W.: 275.39.

Calcd:	C = 74.14	found:	C = 74.24
	H = 9.15		H = 9.20
	N = 5.09		N = 4.92

GLC: 1 m OV 17 column; oven temp. 236 °C; 2.8 atm N_2; retention time 5.25 s.

General procedure for preparing 1-aryl-10-hydroxydecahydroisoquinolines

2.5 g (0.02 mole) 2-(cyclohex-1-enyl)ethylamine was dissolved in 20 ml 1 N HCl and 0.022 mole aromatic aldehyde in 30 ml ethanol was then added. With stirring, the solution was acidified to pH = 2 with 1 N HCl. The reaction mixture was then boiled for 20 h, and the ethanol was distilled off *in vacuo*. The residue was crystallized twice from methanol—acetone, producing 1-aryl-10-hydroxydecahydroisoquinoline hydrochlorides. The analytical samples were crystallized first from 4 N HCl and then from methanol—acetone. All substances were dried for 8 h at 100 °C in vacuo, and analyzed for chloride ion. The analytical and physical data are listed in Table III.

The hydrochlorides were dissolved in hot water, and the solution was made pH = 12 with aq. NaOH. After cooling to room temperature, the crystals were filtered off, dried and recrystallized from methanol or methanol—acetone to give the corresponding amine bases.

For the analyses, the substances were purified by several recrystallizations from the above-mentioned solvents.

Table III

Analytical and physical data on 1-aryl-10-hydroxydecahydroisoquinoline hydrochlorides

Compd.	Formula	M. W.	Anal. (%)		Mp (°C)	Yields (%)
			calcd.	found [b]		
			Cl^-	Cl^-		
IX	$C_{13}H_{19}NO.HCl$	241.762	14.66	14.72	267—269[a]	89
X	$C_{15}H_{21}NO.HCl$	267.800	13.24	13.18	305—307[a]	87
XI	$C_{15}H_{20}N_2O_3.HCl$	312.797	11.33	11.40	286—288[a]	82
XII	$C_{15}H_{20}ClNO.HCl$	302.245	11.73	11.68	304—305[a]	80
XIII	$C_{16}H_{23}NO_2.HCl$	297.826	11.90	11.94	282—284[a]	78
XIV	$C_{17}H_{25}NO_2.HCl$	311.856	11.37	11.42	288—289[a]	75

[a] decomposition
[b] measured potentiometrically

All these bases were dried in vacuo at 100 °C for 8 h and the molecular weights were determined by potentiometric titration in ethanolic solution. The analytical and physical data are given in Table IV. The substances proved pure on TLC (Silica gel G /Reanal/, chloroform—diethylamine 9:1).

Table IV

Analytical and physical data on 1-aryl-10-hydroxydecahydroisoquinolines

Compd.	Formula	M.W.		Anal. (%)						Mp (°C) [b]
		calcd.	found[a]	calcd.			found			
				C	H	N	C	H	N	
IX	$C_{13}H_{19}NO$	205.301	204	76.06	9.33	6.82	76.32	9.07	6.63	192
X	$C_{15}H_{21}NO$	231.339	232	77.88	9.15	6.05	77.60	9.22	5.89	202
XI	$C_{15}H_{20}N_2O_3$	276.336	277	65.20	7.30	10.14	65.34	7.15	9.96	227
XII	$C_{15}H_{20}ClNO$	265.784	266	67.79	7.59	5.27	67.57	7.43	5.40	220
XIII	$C_{16}H_{22}NO_2$	261.365	262	73.53	8.87	5.36	73.27	8.75	5.22	192
XIV	$C_{17}H_{25}NO_2$	275.392	275	74.14	9.15	5.09	74.29	9.02	5.20	196

[a] measured potentiometrically
[b] the materials sublimed before the melting point

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СИНТЕЗ И СТЕРЕОХИМИЯ 1-ЗАМЕЩЁННЫХ-10-ГИДРОКСИДЕКАГИДРОИЗОКИНОЛИНОВ

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Описан простой метод синтеза 1-замещенных-10-гидроксидекагидроизокинолинов через Принс-подобных протон катализированных реакций 2-(циклогексил-1-этил)этиламина с алифатическими, ароматическими и гетероатомными альдегидами. Во всех реакциях получается только олно стереоизомерное (рацемическое) соединение, что было доказано ПМР спектрами.