REACTION OF ALKALI-METAL HYPOHALITES WITH STEREOISOMERIC 2-METHYL-1-ALKYL-2-METHYL-4-ETHYNYLDECAHYDRO-4-QUINOLOLS

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Isomeric 1-alkyl-2-methyl-4-(haloethynyl)decahydro-4-quinolols were synthesized by reaction of the individual stereoisomers of 1-alkyl-2-methyl-4-ethynyldecahydro-4-quinolols with alkali solutions of potassium hypochlorite and hypobromite. 1-Chloro-2-methyl-4-ethynyl decahydro-4-quinolols are formed by the action of an alkaline solution of potassium hypochlorite on isomeric 2-methyl-4-ethynyldecahydro-4-quinolols. Hydrogenolysis of the carbon–halogen bond accompanied by hydrogenation of the C≡C bond was observed under conditions of catalytic hydrogenation of 1,2-dimethyl-4-(haloethynyl)decahydro-4-quinolols. Primarily hydrogenolysis of the nitrogen–halogen bond and subsequent reduction of the acetylenic bond occur in the hydrogenation of 1-chloro-2-methyl-4-ethynyldecahydro-4-quinolols. Replacement of chlorine by hydrogen and subsequent alkylation of the resulting secondary amine and formation of the hydrochlorides of the corresponding N-methyl-substituted acetylenic alcohols occur in the reaction of the chloramines with a mixture of formaldehyde and formic acid.

Data are available regarding the psychotropic activity of compounds of the aliphatic or carbocyclic series containing a halogen atom attached to a triple bond [1]. In this connection the synthesis of similar derivatives in the decahydroquinoline series seemed of interest.

The synthesis of 1-alkyl-2-methyl-4-chloro(bromo)ethynyldecahydro-4-quinolols was accomplished by the method in [2] by reaction of acetylenic alcohols of the indicated series with alkali-metal hypohalites. Thus the isomeric 1,2-dimethyl-4-(haloethynyl)decahydro-4-quinolols (IV-IX and XV-XXI) (Table 1) were obtained by the action of an alkaline solution of potassium hypochlorite or hypobromite on the individual isomers of 1,2-dialkyl-4-ethynyldecahydro-4-quinolols (I-III and X-XIV).

An analysis of the IR spectra of I-XXI showed that the reaction of 1-alkyl-2-methyl-4-ethynyldecahydro-4-quinolols with alkali-metal hypohalites leads to disappearance of the absorption bands at 3320 (≡C–H) and 2120 cm^{-1} (C≡C) characteristic for monosubstituted acetylenic compounds and to the appearance of a band of stretching vibrations of disubstituted C≡C bonds at 2210 cm^{-1}. A distinctive feature of the spectra of the hydrochlorides of the 1-alkyl-2-methyl-4-(haloethynyl)decahydro-4-quinolols is the presence of a number of intense bands at 2400-2700 cm^{-1}, which are observed in the spectra of numerous hydrohalides of compounds of the decahydroquinoline series [3].

Hydrogenolysis of the carbon–halogen bond accompanied by hydrogenation of the triple bond is observed in the reduction of isomeric 1,2-dimethyl-4-(haloethynyl)decahydro-4-quinolols in the presence of the Lindlar catalyst. Thus the addition of 1 mole of hydrogen to IV-IX gives complex mixtures in which the starting haloethynyl derivative, a vinyl alcohol, and their hydrohalides are present. The hydrohalides of the corresponding 4-ethyl-

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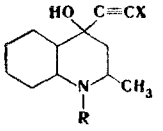
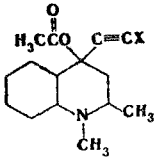
TABLE 1



Compound	Configuration		R	X	mp, °C	Empirical formula	Found, /				Calc., %				Yield, %	Hydrochloride, mp, °C
	CH_3	C≡CX					C	H	Hal	N	C	H	Hal	N		
IV	*a*	*e*	CH_3	Cl	148—149	$C_{13}H_{20}ClNO$	64,7	8,1	14,4	5,7	64,6	8,3	14,7	5,8	47	218—220
V	*e*	*a*	CH_3	Cl	154—155	$C_{13}H_{20}ClNO$	64,4	8,4	14,8	5,8	64,6	8,3	14,7	5,8	38	229—230
VI	*e*	*e*	CH_3	Cl	122—123	$C_{13}H_{20}ClNO$	64,9	8,4	15,1	5,6	64,6	8,3	14,7	5,8	47	162—163
VII	*a*	*e*	CH_3	Br	152—153	$C_{13}H_{20}BrNO$	54,7	7,3	28,0	5,0	54,6	7,0	27,9	4,9	36	225—227
VIII	*e*	*a*	CH_3	Br	169—170	$C_{13}H_{20}BrNO$	54,5	6,9	27,8	5,0	54,6	7,0	27,9	4,9	78	223—224
IX	*e*	*e*	CH_3	Br	133—134	$C_{13}H_{20}BrNO$	54,7	7,0	27,9	5,0	54,6	7,0	27,9	4,9	65	194—195
XV	*e*	*a*	C_2H_5	Cl	119—120	$C_{14}H_{22}ClNO$	65,9	8,4	13,5	5,4	65,7	8,7	13,9	5,5	38	213—214
XVI	*e*	*e*	C_2H_5	Cl	—	$C_{14}H_{22}ClNO \cdot HCl$	57,6	8,0	24,0	4,6	57,5	7,9	24,3	4,8	4	194—195
XVII	*a*	*e*	C_2H_5	Br	117—118	$C_{14}H_{22}BrNO \cdot HCl$	49,6	6,7	34,6	4,0	49,9	6,9	34,3	4,2	30	214—216
XVIII	*e*	*a*	C_2H_5	Br	143—144	$C_{14}H_{22}BrNO \cdot HCl$	49,9	6,9	34,5	4,0	49,9	6,9	34,3	4,2	41	267—269
XIX	*e*	*e*	C_2H_5	Br	146—147	$C_{14}H_{22}BrNO \cdot HCl$	49,9	7,1	34,5	4,2	49,9	6.9	34,3	4,2	30	233—234
XX	*e*	*a*	C_3H_7	Br	140—141	$C_{15}H_{24}BrNO$	56,8	7,5	26,6	4,4	57,3	7,7	25,4	4,5	30	238—240
XXI	*e*	*e*	C_3H_7	Br	158—159	$C_{15}H_{24}BrNO \cdot HCl$	51,4	7,1	32,9	3,7	51,4	7,2	32,9	4,0	24	210—212
XXXI	*a*	*e*	Cl	H	83—84	$C_{12}H_{18}ClNO$	63,4	8,0	15,4	6,1	63,3	8,0	15,6	6,2	72	—
XXXII	*e*	*a*	Cl	H	80—81	$C_{12}H_{18}ClNO$	63,3	8,0	15,6	6,1	63,3	8,0	15,6	6,2	70	—
XXXIII	*e*	*e*	Cl	H	74—75	$C_{12}H_{18}ClNO$	63,3	7.9	15,8	6,2	63,3	8,0	15,6	6,2	72	—

TABLE 2



Compound	Configuration		X	mp, °C	Empirical formula	Found, %				Calc., %				Yield, %	Hydrochloride, mp, °C
	CH_3	~C≡CX				C	H	Hal	N	C	H	Hal	N		
XXII	*a*	*e*	Cl	80—81	$C_{15}H_{22}ClNO_2 \cdot HCl$	56,7	7,0	22,0	4,0	56,5	6,9	22,2	4,4	31	215—216
XXIII	*e*	*a*	Cl	147—148	$C_{15}H_{22}ClNO_2 \cdot HCl$	56,8	7,0	22,4	4,2	56,5	6,9	22,2	4,4	56	204—205
XXIV	*e*	*e*	Cl	63—64	$C_{15}H_{22}ClNO_2 \cdot HCl$	56,7	7,0	22,0	4,1	56,5	6,9	22,2	4,4	44	214—215
XXV	*a*	*e*	Br	141—142	$C_{15}H_{22}BrNO_2$	54,9	6,4	24,3	4,6	55,1	6,4	23,4	4,3	43	217—218
XXVI	*e*	*a*	Br	190—191	$C_{15}H_{22}BrNO_2 \cdot HCl$	49,5	6,2	31,7	3,9	49,6	6,1	31,7	3,8	36	200—201
XXVII	*e*	*e*	Br	126—127	$C_{15}H_{22}BrNO_2$	55,0	6,8	24,5	4,2	55,1	6,4	23,4	4,3	53	211—212

TABLE 3. Conditions for the Acetylation of Stereoisomeric 1,2-Dimethyl-4-(haloethynyl)decahydro-4-quinolols

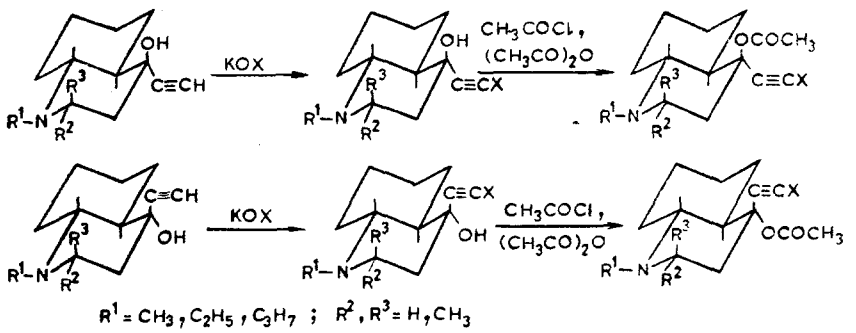
Compound	Configuration		Halogen	Temp, °C	Time, h
	2-CH_3	OH			
IV	*a*	*a*	Cl	110	4
VI	*e*	*a*	Cl	110	3
V	*e*	*e*	Cl	100	3
VII	*a*	*a*	Br	140	20
IX	*e*	*a*	Br	140	4
VIII	*e*	*e*	Br	120	4

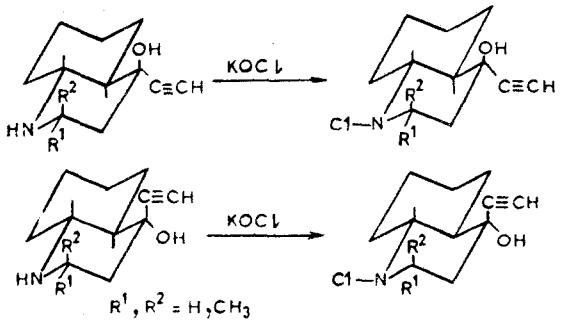
decahydroquinolols are obtained by exhaustive hydrogenation (3 moles of hydrogen) of the same compounds.

The corresponding 4-acetoxydecahydroquinolines (XXII-XXVII) (Table 2) were synthesized by acetylation of isomeric 1,2-dimethyl-4-(haloethynyl)decahydro-4-quinolols (IV-IX) with a mixture of acetyl chloride and acetic anhydride. It should be noted that esterification of bromoethynyl-substituted alcohols VII-IX takes place under more severe conditions than esterification of chlorethynyl-substituted alcohols IV-VI. A difference in the reaction rates is also observed for the epimers of haloethynyl-substituted alcohols: As expected, of the two epimers with respect to the 4 position that have an equatorial methyl group in the 2 position, the epimers with an equatorial hydroxyl group (V and VIII) form an ester more readily, and the epimers with an axial hydroxyl group (VI and IX) form an ester with greater difficulty; alcohols IV and VII, which have an axial hydroxyl group attached to C_4 and an axial methyl group attached to C_2, because of steric interaction of the latter, which hinders approach of the reagent, form esters under more severe conditions (Table 3).

The absorption band of a hydroxyl group is absent in the IR spectra of esters XXII-XXVII, and bands of stretching vibrations of C=O and C–O bonds of acetoxy groups are observed at ~1750 and 1220-1260 cm^{-1}, respectively. An analysis of the form of the band of the C–O bond shows that in the case of epimers with an equatorial acetoxy group (XXIII and XXVI) one observes a band with one absorption maximum at ~1230 cm^{-1}, whereas in the case of epimers with an axial acetoxy group (XXII, XXIV, XXV, and XXVII) one observes bands with two (1227 and 1240 cm^{-1}) or three (1260, 1230, and 1210 cm^{-1}) absorption maxima. These results are in agreement with the available literature data (for example, see [4]).

In the reaction of the isomers of 2-methyl-4-ethynyldecahydro-4-quinolols (XXVIII-XXX) with an alkaline solution of potassium hypochlorite, instead of the expected 2-methyl-4-chloroethynyldecahydro-4-quinolols, we obtained the isomeric 1-chloro-2-methyl-4-ethynyl-decahydro-4-quinolols (XXXI-XXXIII) (Table 1), the N-chloramine structure of which was confirmed by means of spectral methods and also on the basis of a study of their behavior in reactions involving catalytic hydrogenation and with acids. The chloramines obtained in this study on reaction with dry hydrogen chloride gave the hydrochlorides of the starting acetylenic alcohols XXVIII-XXX.





The same result was also observed in the reaction of the chloramines with organic acids and also under conditions of alkylation of the nitrogen atom with a mixture of formaldehyde and formic acid; in the latter case the hydrochlorides of N-methylated acetylenic alcohols I-III are formed. The observed instability of the chloramines in the presence of acids is in agreement with the literature data [5]. Primarily removal of chlorine and subsequent hydrogenation of the triple bond occur in the catalytic hydrogenation of the chloramines in the presence of the Lindlar catalyst.

Absorption bands of a ≡C—H group at 3320 cm^{-1}, a monosubstituted C≡C bond at 2110-2120 cm^{-1}, and an OH bond at 3610-3620 cm^{-1} are present in the IR spectra of chloramines XXXI-XXXIII. The band corresponding to the vibrations of an NH group at 3200-3250 cm^{-1} is absent.

The signals of the proton and methyl group in the 2 position in the PMR spectrum of XXXI-XXXIII are shifted to weaker field as compared with the signals of the same substituents in the spectra of the starting acetylenic alcohols XXVIII-XXX, and this confirms the presence of a polar substituent in the 1 position.

Molecular ion peaks with m/e 227-229 are present in the mass spectra of chloramines XXXI and XXXIII. Characteristic fragments with m/e 210/212, 184/186, and 150 are also observed in the spectrum. The latter fragment makes it possible to determine localization of the chlorine atom in the chloramine molecule and indicates that it is attached to the nitrogen atom.

Further chlorination of the chloramines with potassium hypochlorite in order to obtain their 4-chloroethynyl-substituted derivatives leads only to pronounced resinification of the starting chloramine. The same also occurs in the reaction of potassium hypobromite with 2-methyl-4-ethynyldecahydro-4-quinolols (XXVIII-XXX).

EXPERIMENTAL

The IR spectra of KBr pellets and $1\text{-}3\cdot10^{-2}$ M solutions of the compounds in CCl_4 (layer thickness 0.1 mm) were recorded with a UR-20 spectrometer. The mass spectra were recorded with a Varian MAT-311 spectrometer. The PMR spectra of $CDCl_3$ solutions of the compounds were recorded with a JEOL-100 spectrometer with tetramethylsilane as the standard.

1-2-Dimethyl-4-(chloroethynyl)decahydro-4-quinolol (IV). A chlorinating mixture prepared by bubbling 12 g of chlorine into a solution of 60 g of potassium hydroxide in 200 ml of water was added in small portions (~14 g) with vigorous stirring at 60° to a solution of 1 g (4.8 mmole) of alcohol I in hexane. Each successive portion was added after decolorization of the preceding portion. A total of 140 g of the chlorinating mixture was added. At the end of the reaction, the hexane layer was separated from the aqueous layer, and the latter was extracted repeatedly with ether. The other extracts were combined with the hexane solution and dried with $MgSO_4$. The solvents were removed by distillation, and recrystallization of 1 g of the crude reaction product from hexane gave 0.55 g (47%) of IV with mp 148-149°.

1-2-Dimethyl-4-(bromoethynyl)decahydro-4-quinolol (VIII). A brominating mixture prepared from 11 ml of bromine, 80 g of potassium hydroxide, and 300 ml of water was added in 5-g portions with stirring at 60° to a hexane solution of 0.5 g (2.4 mmole) of alcohol II. After 15 g of the brominating mixture had been added, the reaction mixture was worked up, and the crude product was crystallized from hexane to give 0.55 g (78%) of VIII with mp 169-170°. The remaining 1-alkyl-2-methyl-4-(haloethynyl)decahydro-4-quinolols (V-VII, IX, and

XV-XXI) (Table 1) were similarly synthesized.

1-Chloro-2-methyl-4-ethynyldecahydro-4-quinolol (XXXI). A 14.1-g (7.8 mmole) sample of a chlorinating mixture was added to a solution of 1 g (5.2 mmole) of alcohol XXVIII in hexane, after which the mixture was stirred at 40° for 20 min and at room temperature for 3 h. It was then worked up in the usual manner, and the crude product was recrystallized from hexane to give 0.85 g (72%) of chloramine XXXI with mp 83-84°. Chloroamines XXXII and XXXIII (Table 1) were similarly obtained from acetylenic alcohols XXIX and XXX.

Methylation of 1-Chloro-2-methyl-4-ethynyldecahydro-4-quinolols (XXXI-XXXIII). A total of 0.15 g of crystals with mp 131-132° that did not depress the melting point of decahydroquinolol I was obtained by heating a mixture of 0.3 g (1.3 mmole) of chloramine XXXI, 0.6 g (8 mmole) of 40% formalin, and 0.38 g (7 mmole) of 85% formic acid on a boiling-water bath for 5 h.

Reaction of 0.3 g of chloramine XXXII by the method described above gave 0.1 g of a crystalline substance with mp 132-133°, which was identical to acetylenic alcohol II. Similarly, 0.3 g of XXXIII yielded 0.15 g of crystals with mp 112-113° that did not depress the melting point of ethynylcarbinol III.

Hydrogenation of 1-Chloro-2-methyl-4-ethynyldecahydro-4-quinolols (XXXI-XXXIII). A) The addition of an equimolecular amount of hydrogen to 0.2 g (0.87 mmole) of chloramine XXXI in the presence of the Lindlar catalyst in ethanol gave 0.2 g of crude hydrochloride, decomposition of which in the usual way yielded 0.1 g of a base with mp 118-120°; no melting-point depression was observed for a mixture of this product with acetylenic alcohol XXVIII.

B) The addition of 2 moles of hydrogen to 0.2 g (0.87 mmole) of chloramine XXXI in the presence of $Pd/CaCO_3$ yielded 0.2 g of a hydrochloride, from which 0.1 g of a base with mp 92-94° was isolated; no melting-point depression was observed for a mixture of this base with an authentic sample of 2-methyl-4-vinyldecahydro-4-quinolol (XXXIV) [6].

C) Exhaustive hydrogenation (3 moles of hydrogen) of 0.2 g (0.87 mmole) of chloramine XXXI in the presence of $Pd/CaCO_3$ and subsequent decomposition of the hydrochloride yielded 0.1 g of crystals with mp 86-87°; a mixed-melting-point determination showed that the product was identical to 2-methyl-4-ethyldecahydro-4-quinolol.

The hydrochlorides of the corresponding ethynyl-, vinyl-, and ethyl-substituted alcohols were obtained by selective and exhaustive hydrogenation of chloramines XXXII and XXXIII.

Hydrogenation of 1,2-Dimethyl-4-(haloethynyl)decahydro-4-quinolols (IV-IX). A) A solution of 0.3 g (1.2 mmole) of decahydroquinolol IV in 10 ml of ethanol was hydrogenated in the presence of the Lindlar catalyst. Absorption of 1 mole of hydrogen gave 0.27 g of a mixture, 0.22 g of which was soluble in ether. Chromatography of the mixture of the base and the hydrochloride on activity II Al_2O_3 [ether–petroleum ether (1:2)] yielded 0.1 g of starting chloroethynyl derivative IV and 0.03 g of a substance with mp 120-121° that did not depress the melting point of an authentic sample of 1,2-dimethyl-4-vinyldecahydro-4-quinolol [7].

B) A 0.1-g (0.4 mmole) sample of IV was hydrogenated over $Pd/CaCO_3$ until hydrogen absorption (3 moles) ceased. The hydrogenation product was purified from acetone to give crystals with mp 214-215° that were identical to the hydrochloride of the known 1,2-dimethyl-4-ethyldecahydro-4-quinolol.

Vinyl- and ethyl-substituted alcohols were obtained by selective and exhaustive hydrogenation of the other two stereoisomeric 4-chloroethynyldecahydroquinolols (V and VI). The same alcohols were also formed by hydrogenation of the stereoisomeric 4-bromo-substituted acetylenic alcohols VII-IX.

1,2-Dimethyl-4-(haloethynyl)-4-acetoxydecahydroquinolines (XXII-XXVII). A mixture of 1 g (3.1 mmole) of the hydrochloride of bromo-substituted acetylenic alcohol IX, 12 ml of acetyl chloride, and 30 ml of acetic anhydride was refluxed at 135-140° for 4 h, after which the excess liquid reagents were removed *in vacuo*, and the solid residue was dissolved in 20 ml of water. The aqueous solution was neutralized with potassium carbonate, and the base was extracted with 150 ml of ether. The extract was dried with $MgSO_4$, and the solvent was removed by distillation to give 1.1 g of the crude crystalline acetylation product, purifi-

cation of which from petroleum ether yielded 0.6 g (53%) of acetoxydecahydroquinoline XXVII with mp 126-127°.

Esters XXII-XXVI were similarly synthesized (Table 2).

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OXIDATION OF STEREOISOMERIC N-AMINO-11,14-DICYANOPERHYDROACRIDINES

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The oxidation of trans–syn–trans–N-amino-11,14-dicyanoperhydroacridine with manganese dioxide or bromine gives two stereoisomeric 11,12-dicyanoperhydrofluorenes and two stereoisomeric 2-cyano-1-(2-cyanocyclohexylmethyl)-1-cyclohexenes. The oxidation of trans–anti–cis-N-amino-11,14-dicyanoperhydroacridines with manganese dioxide gives three other stereoisomers of 11,12-dicyanoperhydrofluorene.

It is known [1] that the oxidation of 1,1-disubstituted hydrazines may occur without nitrogen evolution (to give tetrazenes) or with nitrogen evolution. In particular, the oxidation of 2,6-dicyano-1-amino-2,6-dimethylpiperidines (I) with bromine is accompanied by nitrogen evolution and the formation of stereoisomeric 1,2-dicyano-1,2-dimethylcyclopentanes (the products of recombination of the intermediate diradical) and 2,6-dicyano-2-heptane (the product of disproportionation of the diradical) [2].

We carried out the oxidation of stereoisomeric N-amino-11,14-dicyanoperhydroacridines (IIa, b) [3] with active γ-manganese dioxide; the oxidation proceeds smoothly at room temperature and is accompanied by nitrogen evolution. The oxidation of trans–syn–trans isomer IIa leads to two stereoisomeric 11,12-dicyanoperhydrofluorenes (IIIa, b) and two stereoisomeric 2-cyano-1-(2-cyanocyclohexylmethyl)-1-cyclohexenes (IVa, b). The oxidation of trans–anti–cis-isomer IIb gives the three other stereoisomers of 11,12-dicyanoperhydrofluorene (IIIc-e); unsaturated cyanides of IV are not formed here.

Compounds IIIa-e are evidently recombination products, whereas IVa, b are products of disproportionation of the intermediate diradicals.

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