SYNTHESIS AND PROPERTIES OF (3-QUINUCLIDYL)DIARYLCARBINOLS

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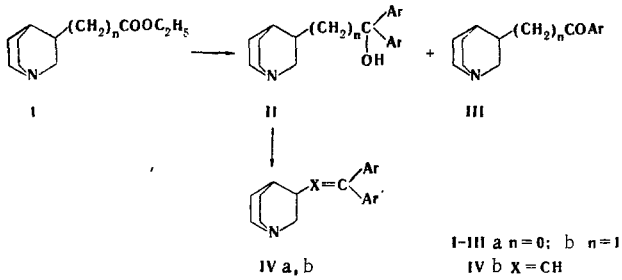
The reaction of 3-ethoxycarbonyl-, 3-ethoxycarbonylmethyl-, and 3-benzoylquinuclidines with organometallic compounds was studied. General methods for the preparation of (3-quinuclidyl)-diarylcarbinols were developed, and the properties of these compounds were studied.

In a study of the biological activity of quinuclidine derivatives it was observed that (3-quinuclidyl)diphenylcarbinol has pronounced antihistamine activity [1]. This compound, under the name fenkarol, has been approved as an antiallergenic agent. Its high activity and the absence of an effect on the central nervous system (CNS) distinguish fenkarol favorably from known antihistamine preparations (dimedrol, pipol'fen, and suprastin). It was necessary to develop general methods for the synthesis of (3-quinuclidyl)diarylcarbinols (II) with identical and different aryl groups in the molecule in order to conduct further studies with variation of the structures of both the quinuclidine and aromatic portions of the fenkarol molecule to investigate the effect of the indicated changes on the biological activity.



I II III

IV a, b

I–III a n=0; b n=1;
IV b X=CH

The simplest method for the preparation of carbinols II with identical aryl groups (Ar=Ar') was reaction of ethyl quinuclidine-3-carboxylate (Ia) [2] and 3-quinuclidylacetate (Ib) [3] with organometallic compounds, and the simplest method for the preparation of carbinols II with different aryl groups was organometallic synthesis from 3-aroylquinuclidines (IIIa, b). In a detailed study of the first method it was observed that in most cases the reaction of esters Ia, b with arylmetals proceeds ambiguously: 3-quinuclidyl aryl ketones (III) are formed along with carbinols II. The direction of the reaction is determined by the structures of both the starting quinuclidine derivative and the aryl component and is evidently associated primarily with steric factors. The reaction of Ia and Ib with phenyllithium proceeds most unambiguously to give practically only carbinols II. The formation of a mixture of II and III is observed when substituents (chlorine atoms and methyl groups) are introduced in the phenyl ring and when they are replaced by thienyl or cyclohexyl rings; this is associated with an increase in the volume of the groupings introduced. In some cases, for example, in the case of a cyclohexyl substituent, ketone III is the primary reaction product of ester Ia with cyclohexylmagnesium bromide. A shift in the reaction to favor the formation of ketones IIIb is also observed on passing from ester Ia to ester Ib. Thus, whereas the ratio of the corresponding carbinols IIa and ketones IIIa is 1:1 in the reaction of Ia with 2-thienylmagnesium bromide and 4-chlorophenylmagnesium bromide, ketones IIIb are primarily formed from ester Ib in analogous reactions. The effect of steric factors on the course of the reactions of esters I with organometallic compounds shows up most distinctly when one compares the reaction

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of ester Ia with 2- and 4-chlorophenylmagnesium bromides and also with 2- and 4-tolyllithium compounds. In both cases the migration of the substituent in the phenyl ring from the 4 to the 2 position is associated with a shift in the reaction to favor the formation of ketones IIIa. In their turn, ketones III, which contain bulky substituents (2-chlorophenyl and cyclohexyl), are capable of undergoing further reaction only with phenyllithium and are converted in this case to carbinols II with mixed groupings. On the other hand, ketones III without substituents in the phenyl ring (for example, 3-benzoylquinuclidine) react with substituted arylmetals to also give carbinols II with different aryl residues. All of this constitutes evidence for a substantial contribution of steric factors to the reaction under study here, whereas one cannot exclude the dependence of the direction of the reaction of esters of quinuclidine carboxylic acids with organometallic compounds on the lability of the carbon–metal bond of the latter. Aryllithium compounds, which are more reactive than arylmagnesium halides, shift the reaction to favor the formation of carbinols II. Thus the yields of carbinol IIa (Ar = Ar' = C_6H_5) are, respectively, 90 and 60% [1] in the reaction of ester Ia with phenyllithium and phenylmagnesium bromide, as compared with 50 and 10% in the reaction with o-tolyllithium and o-tolylmagnesium bromide.

Carbinols IIa with anisyl groups were synthesized by reaction of ester Ia with anisylmagnesium bromide in the presence of 1,2-dibromoethane as the initiator; this reaction could not be realized without the initiator.

Thus our investigation showed that the reaction of esters I and ketones III with organometallic compounds is a sufficiently general method for the synthesis of (3-quinuclidyl)diarylcarbinols with, respectively, identical or different aryl groups.

A further study of the properties of carbinols II and, particularly, their reaction with dehydrating reagents, showed that carbinols containing phenyl, thienyl, and anisyl groupings are dehydrated most readily on brief heating with 85% formic acid. Water is not split out from (3-quinuclidyl)bis(4-chlorophenyl)carbinol and (3-quinuclidyl)di(2-, 3-, and 4-tolyl)carbinols under these conditions. Prolonged heating of the chlorophenyl derivative with thionyl chloride made it possible to obtain 3,3-bis(4-chlorophenyl)methylenequinuclidine, but the tolyl derivatives were not dehydrated by either this method or by heating with sulfuric acid solutions of varying concentration, phosphorus pentoxide, and p-toluenesulfonic acid in xylene with azeotropic removal of water by distillation. The starting carbinols were recovered in all cases. We were also unable to dehydrate (3-quinuclidyl)phenylcyclohexylcarbinol; only replacement of the hydroxyl group by chlorine occurs when this compound is heated with thionyl chloride. The stability of (3-quinuclidyl)ditolyl- and (3-quinuclidyl)phenylcyclohexylcarbinols with respect to dehydrating reagents is probably due to the donor effect of both the cyclohexyl group and the methyl groups bonded to the phenyl rings.

EXPERIMENTAL

(3-Quinuclidyl)diarylcarbinols (IIa). A) A solution of 0.05 mole of Ia in 60 ml of absolute ether was added at 0-5° to an ether solution of aryllithium, obtained from 0.15 mole of aryl bromide and 0.3 g-atom of lithium in 100 ml of ether, and the mixture was allowed to stand at room temperature for 20 h and refluxed for 4 h. It was then cooled and treated with 80 ml of water, and the resulting precipitate was separated, washed with water, and recrystallized. Salts were obtained from the base.

The Ar and Ar' values, the preparative method, the physical constants, the analytical results, and the yields of carbinols II are presented in Table 1.

(3-Quinuclidyl)di(n-butyl)carbinol. This compound, with bp 143-145° (0.6 mm) and mp 74-76° (from hexane), was obtained in 76.5% yield by method A. Found: C 75.7; H 12.2%. $C_{16}H_{31}NO$. Calculated: C 75.8; H 12.3%. The hydrochloride had mp 158-160° (from acetone).

(3-Quinuclidyl)di(n-hexyl)carbinol, with bp 174-176° (0.8 mm), was obtained in 85% yield by method A. The sulfate had mp 124-125° (from ethyl acetate). Found: C 58.6; H 10.1; S 7.8%. $C_{20}H_{39}NO \cdot H_2SO_4$. Calculated: C 58.9; H 10.1; S 7.9%.

B) A solution of 0.05 mole of Ia in 60 ml of ether was added to a solution of arylmagnesium bromide obtained from 0.2 mole of aryl bromide and 0.2 g-atom of magnesium in 100 ml of ether, and the mixture was allowed to stand at 20° for 20 h, after which it was refluxed for 6 h. It was then cooled and treated with 120 ml of 7% hydrochloric acid. The ether solution was separated, and the acid solution was made alkaline with potassium carbonate and extracted with chloroform. The residue remaining after removal of the chloroform was crystallized, and salts were isolated from the base. The 3-quinuclidyl aryl ketones were obtained from the mother liquors by vacuum fractionation or crystallization after separation of the carbinol bases and evaporation. 3-Quinuclidyl 4-chlorophenyl ketone, with mp 93-95° (from heptane), was obtained in 35.4% yield. Found: C 67.4; H 6.3; Cl 14.5%. $C_{14}H_{16}ClNO$. Calculated: C 67.3; H 6.4; Cl 14.2%. 3-Quinuclidyl 2-thienyl

TABLE 1. (3-Quinuclidyl)diarylcarbinols (II)

Ar	Ar'	Method	Base mp, °C	Hydrochloride mp, °C	Empirical formula	Found, %			Calculated, %			Yield, %
						C	H	Cl	C	H	Cl	
2-$CH_3C_6H_4$[a]	2-$CH_3C_6H_4$	A	238–240		$C_{22}H_{27}NO$	82,1	8,5	–	82,2	8,5	–	50
				278–279	$C_{22}H_{27}NO \cdot HCl$	—	—	9,7	—	—	9,9	
3-$CH_3C_6H_4$	3-$CH_3C_6H_4$	A	226–227		$C_{22}H_{27}NO$	82,1	8,4	–	82,2	8,5	–	86
				271–272	$C_{22}H_{27}NO \cdot HCl$	—	—	9,8	—	–	9,9	
4-$CH_3C_6H_4$	4-$CH_3C_6H_4$	A	220–222		$C_{22}H_{27}NO$	82,3	8,3	–	82,2	8,5	–	86,5
				271–272	$C_{22}H_{27}NO \cdot HCl$	—	—	9,7	—	—	9,9	
2-$CH_3OC_6H_4$	2-$CH_3OC_6H_4$	C	—	235–237[b]	$C_{22}H_{27}NO_3 \cdot HBr$	60,9	6,4	18,2[d]	60,8	6,5	18,2[d]	71,5
4-$CH_3OC_6H_4$	4-$CH_3OC_6H_4$	C	—	72–74[c]	$C_{22}H_{27}NO_3 \cdot H_2SO_4 \cdot {}^1/_2H_2O$	57,6	6,8	–	57,4	6,6	–	68
3,4-di-$CH_3C_6H_4$	3,4-di-$CH_3C_6H_4$	A	259–261		$C_{24}H_{31}NO$	82,5	9,0	–	82,5	8,9	–	69,5
				275–276	$C_{24}H_{31}NO \cdot HCl$	—	—	9,0	–	—	9,2	
4-ClC_6H_4	4-ClC_6H_4	B	214–216	198–199	$C_{20}H_{21}Cl_2NO$	66,6	5,9	19,3	66,3	5,8	19,6	50,5
C_4H_3S-2	C_4H_3S-2	B	181–183	233–234	$C_{16}H_{19}NOS_2$	–	–	20,8[e]	–	—	21,0[e]	36,7
C_6H_5	2-$CH_3C_6H_4$	B	242–244		$C_{21}H_{25}NO$	82,0	8,1	–	82,1	8,2	—	51
				303–304	$C_{21}H_{25}NO \cdot HCl$	—	—	9,9	–	—	10,3	77
C_6H_5	4-$CH_3C_6H_4$	D	230–232	278–279	$C_{21}H_{25}NO$	82,0	8,2	–	82,1	8,2	—	
C_6H_5	2-ClC_6H_4	D	208–210		$C_{20}H_{22}ClNO$	72,9	6,9	–	73,3	6,8		51
				283–284	$C_{20}H_{22}ClNO \cdot HCl$	—	—	10,6	—	—	10,8	
C_6H_5	4-ClC_6H_4	E	187–188	275–276	$C_{20}H_{22}ClNO$	73,1	6,8	10,9	73,3	6,8	10,8	41,4
C_6H_5	C_4H_3S-2	E	—	235–236	$C_{18}H_{21}NOS \cdot HCl$	64,1	6,6	10,3	64,4	6,6	10,6	50

[a] 3-Quinuclidyl 2'-tolyl ketone was isolated in 23% yield from the mother liquor after separation of carbinol II.
[b] Hydrobromide.
[c] Sulfate.
[d] Bromine content.
[e] Sulfur content.

TABLE 2. Characteristics of the Compounds Obtained

X	Ar	Ar'	mp, °C, of hydrochlorides (bases)	mp, °C, of the methiodides	Empirical formula	Found, %			Calc., %			Yield, %
						C	H	Cl	C	H	Cl	
CH	C_6H_5	C_6H_5	261—263	217—219	$C_{21}H_{23}N \cdot HCl$	77,4	7,5	10,8	77,4	7,4	10,9	70
—	C_6H_5	C_6H_5	252—254 (134—136)	220—222	$C_{20}H_{21}N$	87,5	7,6	11,2[a]	87,2	7,7	11,4[a]	78
—	2-$CH_3OC_6H_4$	2-$CH_3OC_6H_4$	(123—124)	231—232	$C_{22}H_{25}NO_2$	78,8	7,5	—	78,8	7,5	—	89
—	4-$CH_3OC_6H_4$	4-$CH_3OC_6H_4$	187—188[b]	—	$C_{22}H_{25}NO_2 \cdot H_2SO_4$	61,0	6,5	6,9[c]	61,0	6,3	7,4[c]	82
	C_6H_5	4-ClC_6H_4	244—245	130—132	$C_{21}H_{22}ClN \cdot HCl$	69,6	6,4	19,4	70,0	6,4	19,7	73
—	4-ClC_6H_4	4-ClC_6H_4	300—302	223—224	$C_{20}H_{19}Cl_2N \cdot HCl$	62,9	5,5	27,6	63,1	5,3	27,9	70
—	C_4H_3S-2	C_4H_3S-2	279—281 (96—97)	252—254	$C_{16}H_{17}S_2N$	66,6	5,9	22,4[c]	66,9	5,0	22,3[c]	69

[a] This is the chlorine content in the hydrochloride.
[b] Sulfate.
[c] Sulfur content.

ketone, with bp 153-154° (0.8 mm) and mp 79-81° (from heptane), was obtained in 34% yield. Found: C 65.4; H 6.9; S 14.9%. $C_{12}H_{15}NOS$. C 65.1; H 6.8; S 14.6%.

C) A solution of 0.1 mole of Ia in 100 ml of ether was added at 0-5° to an ether solution of a mixture of organomagnesium compounds obtained from 0.4 mole of anisylmagnesium bromide, 0.4 mole of 1,2-dibromoethane, and 0.8 g-atom of magnesium in 400 ml of ether. The mixture was then treated as in method B. The hydrobromides were precipitated by acidification of the mixture with 7% hydrochloric acid, after which they were converted to the bases by treatment with ammonia.

D) A solution of 0.015 mole of 3-quinuclidyl cyclohexyl or aryl ketone in 30 ml of ether was added at 0-5° to an ether solution of aryllithium, obtained from 0.03 mole of arylbenzene and 0.06 g-atom of lithium in 60 ml of ether, after which the mixture was treated as in method A.

(3-Quinuclidyl)(cyclohexyl)phenylcarbinol. This compound, with mp 192-194°, was obtained in 81.5% yield. Found: C 79.9; H 9.5%. $C_{20}H_{29}NO$. Calculated: C 80.2; H 9.7%.

E) A solution of 0.015 mole of 3-benzoylquinuclidine in 30 ml of ether was added to an ether solution of arylmagnesium bromide, obtained from 0.03 mole of arylbromide and 0.03 g-atom of magnesium in 60 ml of ether, after which the mixture was treated as in method B.

3-Quinuclidyl Cyclohexyl Ketone. A solution of 10 g (0.055 mole) of Ia in 50 ml of ether was added to an ether solution of cyclohexylmagnesium bromide, obtained from 35.6 g (0.218 mole) of cyclohexyl bromide and 5.6 g (0.218 g-atom) of magnesium in 100 ml of ether, after which the mixture was treated as in method B. The chloroform extract of the reaction products was evaporated, and the residue was triturated with ether. The ether solution was filtered to remove the insoluble solids, the ether was removed by distillation, and the residue was vacuum fractionated to give the product, with bp 127-128° (1 mm), in 62.7% yield. Found: C 76.0; H 10.5%. $C_{14}H_{23}NO$. Calculated: C 76.0; H 10.5%.

3-Quinuclidyl 2-Chlorophenyl Ketone. This compound, with bp 157-158° (0.8 mm), was similarly obtained in 53.5% yield. Found: C 67.6; H 6.7%. $C_{14}H_{16}ClNO$. Calculated: C 67.4; H 6.5%.

3-Quinuclidyl 2-Tolyl Ketone. This compound, with bp 160-162° (1.2 mm), was similarly obtained in 42.3% yield. Found: C 78.8; H 8.5; N 6.1%. $C_{15}H_{19}NO$. Calculated: C 78.6; H 8.4; N 6.1%.

3-Quinuclidylmethyl 4-Chlorophenyl Ketone. This compound was obtained by reaction of ester IIb with 4-chlorophenylmagnesium bromide. The precipitate that formed on acidification of the mixture after completion of the Grignard reaction was removed by suction filtration and washed with water to give 71.5% of the hydrobromide with mp 211-213° (from ethanol). Found: C 52.4; H 5.7; Br 23.5%. $C_{15}H_{13}ClNO \cdot HBr$. Calculated: C 52.4; H 5.6; Br 23.2%.

3-Quinuclidylmethyl 2-Thienyl Ketone. This compound was obtained by reaction of ester IIb with 2-thienylmagnesium bromide. The precipitate that formed on acidification of the reaction mixture was removed by suction filtration and washed with water to give the hydrobromide, with mp 225-226° (from methanol), in 51% yield. Found: C 49.5; H 5.8; Br 25.4; S 10.2%. $C_{13}H_{17}NOS \cdot HBr$. Calculated: C 49.4; H 5.7; Br 25.3; S 10.1%.

3,3-Bis(4-chlorphenyl)methylenequinuclidine. A mixture of 5 g (0.014 mole) of (3-quinuclidyl)bis-(4-chlorophenyl)carbinol and 40 ml of thionyl chloride was refluxed for 20 h, after which it was vacuum evaporated, and the residue was made alkaline with potassium carbonate and extracted with chloroform.

1,1-Diphenyl-2-(3-quinuclidyl)ethylene. A solution of 3.07 g (0.01 mole) of (3-quinuclidylmethyl)diphenylcarbinol in 6 ml of 85% formic acid was refluxed for 30 min, after which the formic acid was removed by vacuum distillation, and the residue was made alkaline with potassium carbonate and extracted with benzene. The remaining IV were similarly obtained (see Table 2).

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REACTION OF DIMETHYLAMINES WITH EPIMERIC (AT THE 2 AND 4 POSITIONS) trans-2-METHYL- AND trans-1,2-DIMETHYL-4-VINYLETHYNYLDECAHYDRO-4-QUINOLOLS

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A mixture of the corresponding 4-(4-dimethylamino-1,2-butadienyl)- and 4-(4-dimethylamino-1-butynyl)decahydro-4-quinolols, with predominance of the allene components, is formed from each vinylacetylenic alcohol as a result of the addition of diethylamine to epimeric (at the 2 and 4 positions) trans-2-methyl- and trans-1,2-dimethyl-4-vinylethynyldecahydro-4-quinolols. On the basis of the PMR spectra and data on the stabilities of allenic and acetylenic diamino alcohols under the conditions of their formation, it was concluded that the addition of dimethylamine to 4-vinylethynyldecahydro-4-quinolols proceeds simultaneously via two pathways – at the 1,4 and 3,4 positions of the vinylethynyl substituent.

We have previously shown that some decahydroquinoline derivatives have high physiological activity [1]. Continuing our search for new physiologically active compounds in this series, in the present research we studied the reaction of epimeric (at the 2 and 4 positions) trans-2-methyl- and trans-1,2-dimethyl-4-vinylethynyldecahydro-4-quinolols [2] with dimethylamines.

It is known that lithium dimethylamide readily adds to conjugated vinylacetylenic hydrocarbons to give acetylenic or allenic amines [3]. The addition of lithium dimethylamide to methylvinylacetylene proceeds in

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