SYNTHESIS AND PHARMACOLOGICAL EXAMINATION OF (3-QUINUCLIDYL)-DIPHENYLCARBINOLS SUBSTITUTED IN THE BENZENE RING

M. É. Kaminka, E. E. Mikhlina,
V. Ya. Vorob'eva, A. D. Yanina,
N. A. Komarova, M. D. Mashkovskii,
and L. N. Yakhontov

UDC 615.218.2.012.1

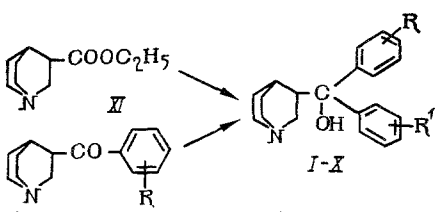
We have previously synthesized and subjected to pharmacological examination a series of quinuclidylcarbinols with differing positions of the diphenylcarbinol group on the atoms of the bicyclic structure, differing distances of this grouping from the quinuclidine nucleus, and differing degrees of saturation of the 1-azabicyclic system. It was shown that one of these compounds, (3-quinuclidyl)diphenylcarbinol, possesses high antihistaminic activity, surpassing in several pharmacological respects the known antihistamine drugs dimedrol and diprazine (dipolfen). Following clinical trials, this compound was approved for the treatment of various allergic conditions, under the name 'fenkarol.'

In continuation of the search for effective antihistamine drugs, and in order to elucidate the relationship between structure and pharmacological activity, it was of interest to prepare and to compare the pharmacological activity of analogs of fenkarol, i.e., (3-quinuclidyl)diphenylcarbinol derivatives containing various substituents in different positions in the benzene rings (I-X). In other series of antihistaminc drugs, the introduction of substituents into the benzene rings, especially a chlorine atom in the para position, often increases activity (suprastin, tavegil, etc.).

Of the compounds of interest to us, the literature describes only one representative, (3-quinuclidyl)-di-4'-methoxyphenyl)carbinol, which like the unsubstituted (3-quinuclidyl)-diphenylcarbinol displays only weak spasmolytic activity. The antihistamine properties of these compounds were not examined.

Carbinols I-VII, in which both the aryl residues are the same ($R=R^1$), were synthesized by reaction of 3-ethoxycarbonylquinuclidine with the appropriate arylmagnesium bromides of aryllithium compounds. The reactions with 2- and 4-anisylmagnesium bromides were satisfactorily accomplished in the presence of 1,2-dibromoethane as initiator.

The carbinols VIII-X, in which the aryl residues were different (RR') were obtained by reaction of organometallic reagents with 3-aroylquinuclidines.



I-X

I: R=R'=2=CH_3; *VI*: R=R'=2=CH_3O
II: R=R'=3=CH_3; *VII*: R=R'=4=CH_3O
III: R=R'=4=CH_3; *VIII*: R=H, R'=2=CH_3
IV: R=R'=3,4=di=CH_3; *IX*: R=2=Cl, R'=H
V: R=R'=4=Cl, *X*: R=H, R'=4=Cl

S. Ordzhonikidze All-Union Scientific-Research Institute of Pharmaceutical Chemistry, Moscow. Translated from Khimiko-Farmatsevticheskii Zhurnal, Vol. 10, No. 9, pp. 22-27, September, 1976. Original article submitted November 27, 1975.

TABLE 1. Pharmacological Properties and Toxicities of (3-Quinuclidyl)-diarylcarbinols (I-X)

Compound	Broncholytic effect*		LD_{50} in mice (mg/kg)
	prevention of the effect of histamine	prevention of the effect of serotonin	
I	2	>2	68
II	>2	>2	43
III	0,2	0,1	49
IV	>2	>2	31
V	>2	>2	57
VI	>2	>2	73
VII	0,2	0,1	22,5
VIII	0,5	0,2	59
IX	0,5	0,5	66
X	>2	>2	43
Fenkarol (R=R'=H)	0,2	1	62

*Doses are given in mg/kg, preventing bronchospasm by 80-90%.

In the pharmacological testing of the compounds, a preliminary selection of the most active members was made by the modified Consett–Rossler method using narcotized guinea pigs [1]. The presence of activity was indicated by the ability of the compounds to prevent bronchospasm caused by repeated (at intervals of 15-20 min) administrations of histamine (5 μg) or serotonin (5 μg/kg). In comparing the activity of the compounds, that dose was selected which reduced bronchospasm by 80-90%; the duration of the effect was judged by the time of reduction of the bronchospasm (not less than 60% of the initial value) on a single administration of the compound and repeated administration of one of the bronchoconstrictors.

The toxicities of the compounds (LD_{50}) were determined in mice by a single intravenous administration, the mean lethal dose being calculated by the method of Kerber.

The results are given in Table 1, from which it will be seen that high antihistamine activity is shown by I, VI, VII, and IX, which are substituted in the ortho position of one or both of the benzene rings by chlorine, methyl, or methoxyl groups, the most active compounds being I and VI, which have ortho substitutents in both benzene rings.

Compounds I and V differ in their mode of action from fenkarol. Fenkarol, in a dose of 0.2-0.5 mg/kg, achieves its maximum antihistaminic broncholytic effect 3 min after administration, the bronchoconstrictor effect of histamine (on repeated dosing) reaching 60% of its initial value after 60-120 min. Compounds I and VI on the other hand, at the same dose rate, had a steadily increasing antihistaminic effect which reached a maximum 40-50 min following administration, and the bronchoconstrictor effect of histamine was reduced to only 12-25% of its initial value for the subsequent 3-4 h of the experiment. Compounds I and VI did not differ in the nature and level of their activity, but I was less toxic in mice.

Moving the substituents in the benzene rings from ortho to the meta, para, or meta,para-disubstituted positions (II-V, VII, X) reduces antihistamine activity by a factor of more than 10 as compared with fenkarol.

The antiserotonin broncholytic activity was also greatest on the ortho-substituted compounds I, VI, VIII, and IX, but in this case the serotonin activity was 10-20 times greater than that of fenkarol. While fenkarol prevents serotonin bronchospasm to the extent of 80-90% in a dose of 1 mg/kg, and its effect lasts for 60-80 min, compounds I and VI prevent bronchospasm in a dose of 0.1 mg/kg, and their maximum antiserotonin activity (the antiserotonin effect also develops 40-60 min after administration) lasts for more than 4 h.

Compounds I and VI, the most active members of the series, were compared more closely with fenkarol. They were administered to non-narcotized guinea pigs as a 2% suspension in 1% carboxymethylcellulose suspension with an intragastric probe, in a dose of 50 mg/kg.

TABLE 2. Extent of the Latent Period of Intoxication and Lethality on Aerosol Inoculation of Guinea Pigs with Histamine Solution at Various Times Following the Administration of the Drugs

Drug (dose 50 mg/kg, intragastric)	Latent period for intoxication (sec) at various periods following administration of drugs			
	1 h	6 h	24 h	48 h
Control	68 (79,9–56,1), mortality 100%	—	—	—
Fenkarol	233 (301,5 – 167,5) mortality 0	180 (287 – 73), mortality 0	82 (95,6 – 68,8), mortality 100%	—
I	211 (238 – 183), mortality 0	>300, mortality 0	189 (248 – 130), mortality 0	95 (73,4 – 59,8), mortality 30
VI	>300, mortality 0	>300, mortality 0	232 (313,7 – 150,3) mortality 0	98,7 (123,1 – 74,3) mortality 75%

Note. Here and in Table 3: > 300 signifies that on continuous inoculation for 300 sec the reaction in question did not occur ($P \leq 0.05$).

TABLE 3. Extent of the Latent Period of Intoxication on Aerosol Inoculation of Guinea Pigs with Serotonin Solution at Various Times Following the Administration of the Drugs

Drug (dose 30 mg/kg, intragastric)	Latent period for intoxication (sec) at various periods following administration of the drugs			
	1 h	6 h	24 h	48 h
Control	65 (58 – 72)	89,5 (105,4 – 73,6)	72 (84,7 – 59,3)	75,0 (90,9 – 59,1)
Fenkarol	229 (333 – 125)	106,5 (170,1 – 42,9)	101,6 (126,5 – 76,7)	—
I	>300	>300	186 (241 – 131)	155 (219 – 91)
VI	>300	>800	236 (306 – 166)	148 (205 – 92)

Continuous administration of a 1% histamine aerosol for 300 sec was carried out at various times after the administration of single doses of the compounds under examination (1, 6, 24, and 48 h). The duration of the latent period and the number of deaths were allowed for. Experiments carried out on 75 guinea pigs showed (Table 2) that compounds I and VI were markedly superior to fenkarol in the duration of the antihistaminic affect (extending up to 48 h following administration of a single dose), and they increased the latent period for intoxication, moderated its symptoms (apnea, clonic-tonic convulsions), and prevented deaths in the animals.

In a dose of 30 mg/kg, administered intragastrically to guinea pigs, I and VI had a prolonged (greater than 48 h) antisertonin effect, extended the latent period for intoxication on aerosol administration of a 1.5% serotonin solution, and were much superior to fenkarol in the duration of their effects. The results of experiments on 55 guinea pigs are summarized in Table 3.

The effects of fenkarol, I, and VI on the appearance of anaphylactic reactions induced by subplantar administration to non-narcotized rats of 0.1 ml of 6% dextran solution [2] were examined following intragastric administration in a dose of 50 mg/kg. The intensity of the reaction was estimated by the increase in splayfoot caused by edema. Measurements were carried out 30 min after administration of the dextran. The compounds were administered in carboxymethylcellulose suspension 1 h and 24 h before the dextran. The results of experiments on 40 white rats are summarized in Table 4. It will be seen that one hour after administration, all three compounds displayed an intense antianaphylactic effect which substantially reduced the development of edema in the paws.

A substantial protective effect was still displayed by I and VI after 24 h, and the prevention of the development of dextran edema was statistically significant. It has been

TABLE 4. Effect of the Drugs on the Anaphylactic Reaction in Rats*

Drug (dose 50 mg/kg intragastric)	Increase in splayfoot (mm) at various times after administration of drugs	
	1 h	24 h
Control	3,70 (2,76 – 4,64)	3,54 (2,81 – 4,27)
I	0,66(0,08 – 1,24)	1,14 (0,45 – 1,83)
VI	0,72 (0,14 – 1,30)	1,78 (0,96 – 2,54)
Fenkarol	1,26 (0,67 – 1,85)	3,32 (2,47 – 4,13)

*Increase in splayfoot in the rear extremities following subplantar administration of a 6% solution of dextran; $P \geq 0.05$.

TABLE 5. Effect of Some Antihistamine Drugs and (3-Quinuclidyl)diarylcarbinols on the Duration of the Hypnotic Effect of Hexenal in Mice

Drug (dose 25 mg/kg subcutaneous)	Duration of the hypnotic effect of hexenal (min)
Dimedrol	189 (244 – 134)
Suprastin	228 (280 – 174)
Diprazin (dipolfen)	>300
Control	133,4 (171,1 – 96,7)
Fenkarol	96 (130 – 62)
I	117 (115 – 59)
VI	129 (179 – 79,9)

TABLE 6. (3-Quinuclidyl)diarylcarbinols (I-X)

Compound	Yield, %	Melting point, deg	Found, %			Molecular formula	Calculated, %		
			C	H	Cl		C	H	Cl
I	50	238 – 40*	82,08	8,48	—	$C_{22}H_{27}NO$	82,19	8,46	—
Hydrochloride of I	—	278 – 9	—	—	9,65	$C_{22}H_{27}NO \cdot HCl$	—	—	9,9
II	86	266 – 7	82,11	8,44	—	$C_{22}H_{27}NO$	82,19	8,46	—
Hydrochloride of II	—	271 – 2	—	—	9,82	$C_{22}H_{27}NO \cdot HCl$	—	—	9,9
III	86,5	220 – 2†	82,11	8,44	—	$C_{22}H_{27}NO$	82,19	8,46	—
Hydrochloride of III	—	271 – 2	—	—	9,73	$C_{22}H_{27}NO \cdot HCl$	—	—	9,9
IV	69,5	259 – 61‡	82,46	9,0	—	$C_{24}H_{31}NO$	82,47	8,94	—
Hydrochloride of IV	—	276 – 6	—	—	9,0	$C_{24}H_{31}NO \cdot HCl$	—	—	9,18
V	50,5	214 – 6†	66,56	5,95	19,28	$C_{20}H_{21}Cl_2NO$	66,30	5,84	19,57
Hydrochloride of V	—	198 – 8	—	—	26,58	$C_{20}H_{21}Cl_2NO_3 \cdot HCl$	—	—	26,52
Hydrochloride of VI	71,5	235 – 7*	60,93	6,43	18,18 (Br)	$C_{22}H_{27}NO_3HBr$	60,83	6,5	18,39 (Br)
Sulfate of VII	68	72 – 4*	57,60	6,81	6,64 (S)	$C_{22}H_{27}NO_3 \cdot H_2SO_3 \times \times {}^1/_2H_2O$	57,38	6,56	6,95 (S)
VIII	77	242 – 4*	82,02	8,15	—	$C_{21}H_{25}NO$	82,05	8,19	—
Hydrochloride of VIII	—	303 – 4	—	—	9,98	$C_{21}H_{25}NO \cdot HCl$	—	—	10,30
IX	51	208 – 10	72,92	6,94	—	$C_{20}H_{22}ClNO$	73,29	6,76	—
Hydrochloride of IX	—	283 – 4*	—	—	19,22	$C_{20}H_{22}ClNO \cdot HCl$	—	—	19,46
X	41,4	187 – 8	73,1	6,8	10,9	$C_{20}H_{22}ClNO$	73,3	6,8	10,8
Hydrobromide of X	—	275 – 6*	—	—	19,28	$C_{20}H_{22}ClNO \cdot HCl$	—	—	19,46

*From ethanol.
†From a mixture of acetone and ethanol.
‡From dimethylformamide.

observed previously that among the antihistaminic drugs used in clinical practice (dimedrol, diprazin, suprastin, etc.), fenkarol was outstanding in the absence of depressive effects on the central nervous system. In order to determine whether this advantage was retained by I and VI, their effect was examined on the duration of the hypnotic effect of hexenal. Hexenal was administered to mice intramuscularly in a dose of 100 mg/kg, and I, VI, fenkarol, dimedrol, diprazin, and suprastin subcutaneously in a dose of 30 mg/kg 1 hour before administration of the hexenal. The results (Table 5) indicated that, in contrast to dimedrol, diprazine (dipolfen), and suprastin, the (3-quinuclidyl)diarylcarbinols (fenkarol, I, and VI) did not increase the duration of the hypnotic effects of hexenal, implying the absence of a sedative effect.

Thus, introduction of ortho substituents into both of the benzene rings of (3-quinuclidyl)diphenylcarbinols substantially increased their antoserotonin activity, and the duration of their antihistaminic and antianaphylactic effects. As in fenkarol itself, the ortho-substituted analogs had no depressive effects on the central nervous system.

EXPERIMENTAL

(3-Quinuclidyl)-di-(4'-tolylcarbinol) (III). A solution of 8 g of 3-ethoxycarbonylquinuclidine (XI) in 60 ml of ether was added at 0-5° to an ethereal solution of 4-tolyllithium, obtained from 22.5 g of 4-bromotoluene and 1.84 g of lithium in 60 ml of ether. The mixture was kept for 20 h at 20°, then treated with water. The precipitate was filtered off, washed with water and ether, and recrystallized. Compounds I, II, and IV were obtained similarly (Table 6).

(3-Quinuclidyl)-di-(4'-chlorophenylcarbinol) (V). A solution of 7.7 g of the ester XI in 60 ml of ether was added with cooling at 0-5° to an ethereal solution of 4-chlorophenylmagnesium bromide, obtained from 32.3 g of 4-chlorobromobenzene and 4.1 g of magnesium in 160 ml of ether. The mixture was stirred at a boil for 6 h, cooled, and treated with 100 ml of 7% hydrochloric acid. The ether layer was separated, and the acid solution was basified with potassium carbonate and extracted with chloroform. The residue after removal of the chloroform was recrystallized.

(3-Quinuclidyl)-di-(2'-methoxyphenyl)carbinol (VI). A solution of 20 g of the ester XI in 100 ml of ether was added at 0-5° to an ethereal solution of a mixture of organomagnesium compounds obtained from 81.6 g of 2-methoxybromobenzene, 81.6 g of 1,2-dibromoethane, and 21.2 g of magnesium in 400 ml of ether. The mixture was kept for 20 h at 20°, boiled for 4 h, cooled, and treated with a 7% solution of hydrochloric acid. The hydrobromide of carbinol VI which separated was filtered off and washed with water. The free base was obtained from the hydrobromide by treatment with aqueous ammonia. Compound VII was obtained similarly.

(3-Quinuclidyl)phenyl-(2'-chlorophenyl)carbinol (IX). A solution of 2.5 g of 3-(2'-chlorobenzoyl)quinuclidine in 30 ml of ether was added to an ethereal solution of phenyllithium, obtained from 3.14 g of bromobenzene and 0.56 g of lithium in 60 ml of ether. The mixture was stirred for 20 h, and treated with water.

(3-Quinuclidyl)phenyl-(4'-chlorophenyl)carbinol (X). A solution of 2.7 g of 3-benzoylquinuclidine in 30 ml of benzene was added at 0.3° to a solution of 4-chlorophenylmagnesium bromide, obtained from 6 g of 4-chlorobromobenzene and 0.75 g of magnesium in 80 ml of ether. The mixture was boiled for 6 h, cooled, and treated with a 7% solution of hydrochloric acid. The organic layer was separated, and the aqueous layer was basified and extracted with chloroform. The residue after removal of the solvent was recrystallized from ethanol.

(3-Quinuclidyl)phenyl-(2'-tolyl)carbinol (VIII). This was obtained by the reaction of 3-benzoylquinuclidine with 2-tolyllithium. The reaction was carried out as in the preparation of III.

The yields, melting points of the free bases and their salts, and analyses for compounds I-X are given in Table 6.

LITERATURE CITED

1. M. É. Kaminka, Farmakol. Toksikol., No. 2, 229-231 (1975).
2. J. R. Perrat and G. B. West, J. Physiol. (Lond.), 137, 179-192 (1957).