SYNTHESIS AND PHARMACOLOGICAL INVESTIGATION OF 3-QUINUCLIDYL DIALKYL, DIHETERYL, AND CYCLOALKYLARYL CARBINOLS

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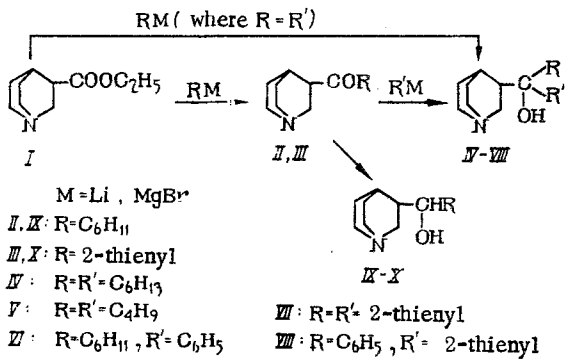
In view of the pronounced pharmacological activity of the antihistamine fenkarol (the hydrochloride of 3-quinuclidyl diphenyl carbinol), which has been accepted as a drug for the treatment of various allergic ailments [1], we have previously synthesized various analogs of this compound and subjected them to pharmacological studies. We studied quinuclidyl diphenyl carbinols in which the diphenyl carbinol group was located on various positions of the bicyclic ring, and at various distances from it; we also studied compounds with various degrees of unsaturation in the 1-azabicyclic system [1] and with substituents at various positions of the phenyl ring. Through this work it was shown that introduction of ortho substituents into the phenyl rings leads to a prolongation of antihistamine, antiserotonin, and antiallergic action in comparison with fenkarol.

With the objective of seeking preparations which were more effective for the treatment of allergic diseases and determining the relationship between structure and pharmacological activity in a series of substituted quinuclidyl carbinols, we synthesized and investigated compounds of this type (IV-X), containing alkyl, cycloalkyl, or heteroaryl groups in the carbinol portion of the molecule in place of the aryl residues.

The synthesis of tertiary quinuclidine alcohols (IV-VIII) was accomplished by analogy with the general method which we developed earlier for obtaining 3-quinuclidyl diaryl carbinols from quinuclidine-3-carboxylic acid esters and organometallic compounds.



By the reaction of 3-carbethoxyquinuclidine (I) with butyl- and hexyllithium, we have obtained in high yields the corresponding tertiary alcohols IV and V. A parallel reaction of ester I with 2-thienylmagnesium bromide does not follow the same course: Along with carbinol VII, 3-quinuclidyl cyclohexyl ketone (III) comprises 40% of the total product. In the reaction of ester I with cyclohexylmagnesium bromide, practically the only product is 3-quinuclidyl cyclohexyl ketone (II). Ketones II and III were used as starting materials for the synthesis of 3-quinuclidyl cyclohexyl carbinol (IX) and 3-quinuclidyl 2'-thienyl carbinol (X), and also for the synthesis of tertiary alcohols with different R and R' groups (VI and VIII). In the first instance, ketones II and III were reduced catalytically or by complex metal hydrides; in the second case, 3-quinuclidyl cyclohexyl ketones and 3-benzoylquinuclidine were treated with organometallic compounds.

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TABLE 1. Results of the Pharmacological Investigation of Compounds IV-X

Compound	R	R'	Decrease in bronchospasm, % control		LD_{50}, mg/kg
			histaminic bronchospasm	serotonin bronchospasm	
Fenkarol	C_6H_5	C_6H_5	90	90	62
IV	C_6H_{13}	C_6H_{13}	20	0	37
V	C_4H_9	C_4H_9	20	0	60
VI	C_6H_{11}	C_6H_5	80	50	67
VII	Thienyl 2	Thienyl 2	90	40	71,5
VIII	Thienyl 2	C_6H_5	75	35	65
IX	C_6H_{11}	H	40	0	72
X	Thienyl 2	H	15	0	205

RESULTS OF PHARMACOLOGICAL INVESTIGATION

Investigation of the broncholytic properties of the substances which we synthesized was carried out, as in the preceding work [1], on narcotized guinea pigs, by the use of the modified Konzett–Rossler method [2]. Bronchospasm was produced by intravenous administration of histamine (5 mg/kg), serotonin (5 mg/kg), and acetylchloine (10 mg/kg). The investigated compounds were administered intravenously in the form of aqueous solutions of their hydrochlorides or other salts. The broncholytic activity of the compounds was determined by the decrease (in %) of the reaction to the administration of bronchoconstrictors within 3 min after administration of the test compounds; duration of broncholytic action was determined by measuring the time required for restoration of bronchospasm to 50-60% of the control value with repeated administrations of bronchoconstrictors at intervals of 15-20 min.

In the investigation of antihistaminic activity by this method, all compounds were administered at a dose of 0.2 mg/kg; in the study of antiserotonin activity, they were administered at a dose of 1 mg/kg (fenkarol at these doses reduces bronchospasm from histamine and serotonin by 90%).

Cholinolytic activity was tested by administration of the preparations at a dose of 1 mg/kg.

Toxicity of the compounds was determined on mice by intravenous administration; the LD_{50} were calculated by Kerber's method.

The results of the investigation of antihistamine and antiserotonin activity, as well as the toxicities of the compounds, are shown in Table 1.

As shown in Table 1 with replacement of the two phenyl groups in fenkarol by thienyl groups (compound VII), the high antihistaminic activity which is characteristic for fenkarol is preserved; replacement of only one phenyl group by a thienyl group (compound VIII) is accompanied by a slight decrease in activity; transformation to the secondary alcohol 3-quinuclidyl 2'-thienyl carbinol (X) practically destroys the antihistamine and antiserotonin activity of the compound, but leads to the appearance of elements of quinolytic activity. Replacement of the aryl or heteroaryl groups by alkyl (compounds IV and V) is accompanied by significant reduction of antihistaminic activity, since the number of carbon atoms in the aliphatic chain has essentially no significance. It is interesting to note that the transition from the corresponding hexyl derivative (IV) to the cyclohexyl derivative (IX) is accompanied by the emergence of distinct antihistaminic activity, which increases with the introduction of a second cyclic group — the phenyl group (compound VI) — into the carbinol portion of the molecule.

The duration of antihistiminic activity of compound VII is practically indistinguishable from that of fenkarol: Its effect lasts for about 1.5 h, while that of other active compounds does not last more than 45 min.

The shortest-acting antihistaminic effect is that of IX: This lasts for 15 min.

Only VI, VII, and VIII have antiserotonin activity; these contain two cyclic groups in the carbinol portion of the molecule. However, all three preparations are inferior to fenkarol in this regard.

The majority of the compounds, like fenkarol, do not show cholinolytic activity on the bronchospasm model. Only X, at a dose of 1 mg/kg, shows an extremely weak cholinolytic effect, diminishing the bronchoconstrictor action of acetylcholine by 30-40%; atropine at a dose of 0.001 mg/kg in these experiments reduces the acetylcholine bronchospasm by more than 90%.

Compounds V-IX differ little in LD_{50}. As Table 1 indicates, their toxicity does not correlate with antihistamine or antiserotonin activity. Compound X, whose weak antihistaminic activity is combined with cholinolytic properties, is the least toxic. Compound IV, for which the LD_{50} is only one half that of V, does not differ in activity from V.

Like fenkarol, and in contrast to a group of known antihistamines (dimedrol, diprazine, suprastin, diazoline), compounds V, VI, VII, VIII, and IX, which have antihistaminic properties, do not produce stimulant or depressant effects on the central nervous system. Thus, they have little influence on the general state and behavior of the animals, even at doses approaching one half the LD_{50}; in experiments on mice, when the indicated preparations were administered subdermally at a dose of 25 mg/kg 30 min after administration of hexenal (100 mg/kg intraperitoneally), no statistical shortening or lengthening of the duration of activity in comparison with the control animals was found, whereas dimedrol and especially diprazine in these experiments significantly lengthened the action of hexenal.

Thus, our research allows us to conclude that various substituted 3-quinuclidyl carbinols which contain both aryl and heteroaryl or cyclohexyl in the carbinol portion of the molecule have significant antihistaminic activity. The determining factor for manifestation of antihistaminic activity is apparently the cyclic character of these groups. Opening of the rings and conversion to aliphatic compounds is accompanied by a sharp decrease in antihistaminic action. The feature which is peculiar to 3-quinuctidyl carbinol derivatives which have antihistaminic activity is the absence of the marked influence on the functioning of the central nervous system which is characteristic of other known antihistaminic preparations — dimedrol ([2-(diphenylmethoxy)ethyl]dimethylamine) doprazine, suprastin (chloropyramine), etc.

EXPERIMENTAL

Chemistry

3-Quinuclidyl Dibutyl Carbinol (V). A solution of 2.93 g 3-carbethoxyquinuclidine (I) in 30 ml ether was added at 0-3° to an ethereal solution of butyl lithium which had been prepared from 8.8 g butyl bromide and 0.9 g lithium in 60 ml ether. The mixture was kept at room temperature for 20 h, heated at reflux for 4 h, cooled, and treated with 30 ml water. The ethereal layer was separated, and the alkaline aqueous layer was extracted with ether. The combined ether solutions were dried with magnesium sulfate. The residue after evaporation of the ether was dissolved in 10 ml hexane. On standing, carbinol V precipitated. Yield, 2.1 g (50%), mp 74-76° (from hexane). Found, %: C 75.66; H 12.22. $C_{16}H_{31}NO$. Calculated, %: C 75.83; H 12.33.

Hydrochloride. This had mp 164-166° (from a mixture of acetone and ethanol). Found, %: Cl 12.08. $C_{16}H_{31}NO \cdot HCl$. Calculated, %: Cl 12.23.

3-Quinuclidyl Dihexyl Carbinol (IV). This was obtained by the reaction of ester I and hexyl lithium in a reaction analogous to the preparation of carbinol V. The ethereal extract of the reaction products was distilled in vacuum. Yield, 85.5%; bp 174-176° (0.8 mm).

Sulfate. This has mp 124-145° (from ethyl acetate). Found, %: C 58.64; H 10.06; S 7.83. $C_{20}H_{39}NO \cdot H_2SO_4$. Calculated, %: C 58.93; H 10.13; S 7.86.

3-Quinuclidyl Cyclohexyl Ketone (II). A solution of 8.3 g I in 50 ml ether was added at 0-3° to cyclohexyl magnesium bromide which had been prepared from 37.75 g cyclohexyl bromide and 4.9 g magnesium in 130 ml ether. The mixture was kept at room temperature for 20 h and at reflux for 7 h; it was then cooled and treated with 60 ml water, and then 75 ml 7% hydrochloric acid. The ethereal layer was separated, and the aqueous layer was made alkaline with potassium hydroxide and extracted with benzene. The residue after removal of the benzene was distilled in vacuum. Yield 5.3 g (53%), bp 127-128° (1 mm). Found, %: C 76.03; H 10.52. $C_{14}H_{23}NO$. Calculated, %: C 75.97; H 10.48.

Reaction of 3-Carbethoxyquinuclidine (I) with 2-Thienyl Magnesium Bromide. A solution of 10 g I in 100 ml ether was added to 2-thienyl magnesium bromide (prepared from 32.7 g

2-bromothiophene and 4.8 g magnesium in 140 ml ether). The reaction was carried out as described in the previous experiment. During treatment of the reaction mixture with hydrochloric acid a precipitate formed, which was filtered off, washed with water, and recrystallized from 100 ml methanol, to give 4.2 g (25.8%) of 3-quinuclidyl di(2'-thienyl)carbinol (VII), mp 181-183°. Found, %: S 20.84. $C_{16}H_{19}NOS_2$. Calculated, %: S 20.99.

Hydrochloride. This had mp 233-234° (dec.). Found, %: Cl 10.11; S 18.65. $C_{16}H_{19}NOS_2 \cdot HCl$. Calculated, %: Cl 10.36; S 18.75.

The methanolic mother liquors remaining after separation of carbinol VII were evaporated, and the residue was recrystallized from heptane, giving 3.1 g (25.8%) 3-quinuclidyl 2'thienyl ketone (III), mp 79-81°. Found, %: C 65.41; H 6.89; S 14.78. $C_{12}H_{15}NOS$. Calculated, %: C 65.12; H 6.83; S 14.48.

3-Quinuclidyl Cyclohexyl Phenyl Carbinol (VI). A solution of 3.8 g 3-quinuclidyl cyclohexyl ketone in 30 ml ether was added to phenyl lithium (prepared from 6.8 g bromobenzene, and 0.6 g lithium in 60 ml ether). The reaction was carried out in a manner analogous to the synthesis of carbinol V. When the reaction mixture was treated with water, VI precipitated. Yield, 4.2 g (82%); mp 192-194° (from a mixture of ethyl acetate and ethanol). Found, %: C 79.86; H 9.54. $C_{20}H_{29}NO$. Calculated, %: C 80.22; H 9.76.

Hydrochloride. This has mp 280-281°. Found, %: Cl 10.33. $C_{20}H_{29}NO \cdot HCl$. Calculated, %: Cl 10.55.

3-Quinuclidyl 2'- Thienyl Phenyl Carbinol (VIII). A solution of 3 g 3-benzoylquinuclidine in 30 ml ether was added to 2-thienyl magnesium bromide (prepared from 5.67 g 2-bromothiophene and 0.84 g magnesium in 60 ml ether). The reaction was carried out in a manner analogous to the synthesis of ketone II, but without heating. The reaction product was extracted with chloroform. Compound VIII was obtained as the free base in a yield of 2.1 g (50.5%); this was converted to the hydrochloride by the addition of an alcoholic solution of hydrogen chloride. It has mp 235-256°. Found, %: C 64.15; H 6.56; Cl 10.19; S 9.44. $C_{18}H_{21}NOS \cdot HCl$. Calculated, %: C 64.36; H 6.59; Cl 10.56; S 9.54.

3-Quinuclidyl Cyclohexyl Carbinol (IX). A solution of 1.9 g ketone II in 40 ml ethanol was reduced in the presence of 0.15 g platinum oxide at room temperature and the pressure of a 20- to 30-cm column of water. After absorption of one equivalent of hydrogen, the platinum was filtered off, the alcohol was distilled in vacuum, and the residue triturated with ether. Yield 1.55 g (81.5%); mp 152-153° (from acetone). Found, %: C 74.42; H 11.20; N 6.23. $C_{14}H_{25}NO$. Calculated, %: C 75.28; H 11.28; N 6.27.

Hydrochloride. This has mp 229-230°. Found, %: Cl 13.72. $C_{14}H_{25}NO \cdot HCl$. Calculated, %. Cl 13.64.

3-Quinuclidyl 2'-Thienyl Carbinol (X). A solution of 2 g ketone III in 20 ml benzene was added to a suspension of 1 g lithium aluminum hydride in 20 ml ether. The mixture was stirred at reflux for 6 h, cooled, treated with 2 ml water, and filtered. The precipitate was extracted with hot chloroform. The combined solutions were evaporated, and the residue triturated with ether. Yield 1.6 g (80%); mp 184-186° (from ethanol). Found, %: C 64.60; H 7.70; S 14.35. $C_{12}H_{17}NOS$. Calculated, %: C 64.54; H 7.67; S 14.36.

Citrate. This has mp 47-49°. Found, %: C 52.27; H 6.28; S 7.38. $C_{12}H_{17}NOS \cdot C_6H_8O_7$. Calculated, %: C 52.04; H 6.06; S 7.71.

LITERATURE CITED

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