SYNTHESIS AND PHARMACOLOGICAL INVESTIGATION OF QUINUCLIDINE ANALOGS OF SULPIRIDE AND BITIODIN

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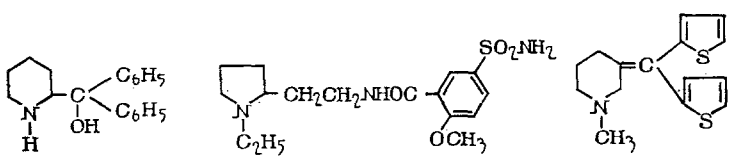
Our earlier research has shown that quinuclidines have far greater activity on cholinergic and histaminergic systems than the analogous aliphatic or monocyclic amines [1]. Evidently, the essential feature of the quinuclidines, to a significant degree, is the presence of a bridgehead nitrogen atom with a spatially unhindered free electron pair. The high reactivity of this electron pair apparently insures facile interaction of the quinuclidine with electrophilic centers of cholinergic or histaminergic receptors and favors the formation of very strong bonds. These theoretical premises have found practical application in the creation of effective drugs: acelidine, oxylidine, temequin, fenkarol, and others.

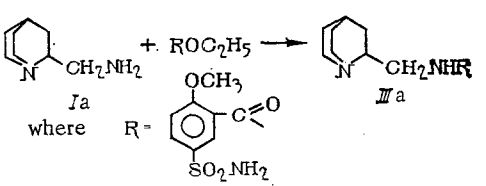
From the theoretical point of view there is significant interest in attempting to determine how much of the regularity that is found for substances which influence choline and histamine receptors will be preserved in other classes of drugs with different mechanisms of action.

The absence of psychostimulatory activity in quinuclidinyldiarylcarbinols [2], and particularly in quinuclidinyl-2-diphenylcarbinol, the quinuclidine analog of the piperidine derivative Piridrol (pipradrol, meratran) — a well-known central nervous system stimulator — has shown, in fact, that the relationships which were found for choline and histamine receptors are not applicable to certain other biochemical receptors. In order to study these problems further, we synthesized and screened quinuclidine analogs of two other drugs which affect the inner portion of the central nervous system: the antiemetic sulpiride — 1-ethyl-2-(2'-methoxy-5'-sulfamidobenzoylaminoethyl)pyrrolidine — and the cough suppressant bitiodin — 1-methyl-3-bis(2'-thienyl)methylenepiperidine. Along with the quinuclidine analogs of these drugs, we also synthesized and screened some other structurally related aza- and diazabicyclic compounds.



Piridrol Sulpiride Bitiodin

The synthesis of aza- and diazabicyclic analogs of sulpiride with nitrogen in the bridgehead position (III) was carried out according to the following scheme:

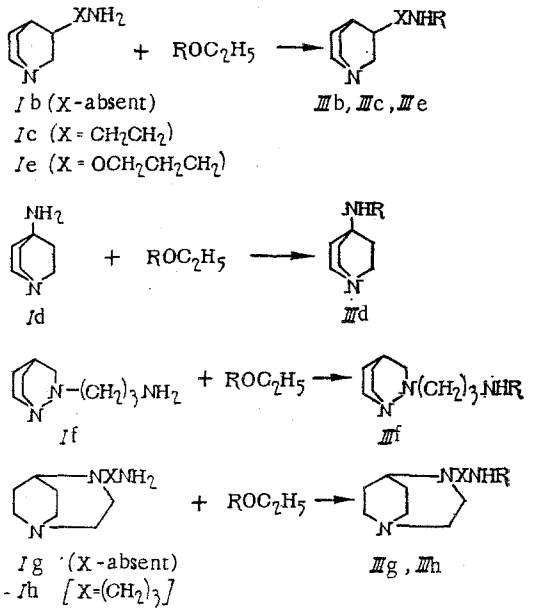


Ia

where R =

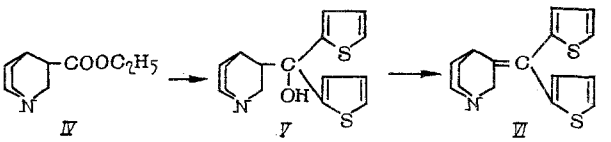
IIIa

S. Ordzhonikidze All-Union Scientific-Research Institute of Pharmaceutical Chemistry, Moscow. Translated from Khimiko-Farmatsevticheskii Zhurnal, Vol. 10, No. 11, pp. 56-60, November, 1976. Original article submitted February 17, 1976.



In all, eight compounds in this series were synthesized and screened (see Table 1).

Synthesis of the quinuclidine analog of bitiodin was accomplished by the following scheme:



We converted 3-carbethoxyquinuclidine (IV), by reaction with 2-thienylmagnesium bromide, to 3-quinuclidinyl-di(2'-thienyl)carbinol (V), which underwent dehydration on boiling with 85% formic acid to give di(2'-thienyl)-3-methylenequinuclidine (VI).

EXPERIMENTAL

Pharmacology

Pharmacological investigation of the group of compounds of general structure III was carried out in comparison with sulpiride, which is a powerful antagonist of emetic substances in animal experiments. Antiemetic activity was investigated on cats by intramuscular treatment with compound III at a dose of 3 mg/kg followed by subcutaneous injection of apomorphine at a dose of 25 mg/kg; the latter is sufficient to provoke vomiting (often repeatedly) in all the experimental animals. In tests on cats, Aminazine administered intramuscularly at a dose of 3 mg/kg shows distinct antiemetic action. Each of the compounds of group III which were under investigation were administered to three animals; in a parallel control experiment the same number of cats were treated with apomorphine alone. It was established that none of the type III compounds investigated had antiemetic activity.

The toxicity of the compounds was determined by intravenous injection of aqueous solutions into white mice weighing 16-17 g (see Table 1). As regards the general activity of the investigated substances, we observed the development of partial to complete paralysis of the extremities, lassitude, and reduced respiration; this was followed by cessation of respiration and soon after by cessation of heart activity.

The compounds of group III do not prevent the development of nicotine-induced tremors in mice, nor do they prevent the development of convulsive symptoms from the injection of Korazole, strychnine, or Arecoline, or from electric shock.

TABLE 1. 2-Methoxy-5-sulfamidobenzoyl Derivatives of 1-Aza- and Diazabicycloalkanes

Compound	Method of isolation	Yield, %	Melting point, deg	Found, %				Empirical formula	Calculated, %				LD_{50} (white mice, intravenously)
				C	H	N	S		C	H	N	S	
IIIa	a	83,4	149—50	53,27	6,74	—	9,01	$C_{16}H_{23}N_3O_4S \cdot 1/2H_2O$	53,20	6,68	—	8,84	29,7
IIIb	a	97	235—6 (dec.)	52,82	6,32	12,43	9,47	$C_{15}H_{21}N_3O_4$	53,02	6,26	12,43	9,45	185,0
IIIc	b	93	255—6 (dec.)	55,61	6,80	11,65	8,72	$C_{17}H_{25}N_3O_4$	55,56	6,89	11,44	8,73	41,0
IIId	b	92	60—1 (dec.)	51,86	6,41	—	9,23	$C_{15}H_{21}N_3O_4 \cdot 1/2H_2O$	51,62	6,33	—	9,20	415,0
IIIe	b	86	142—3 (dec.)	54,50	7,51	—	6,89	$C_{18}H_{27}N_3O_5S \cdot C_2H_5OH$	54,16	7,49	—	7,23	9,3
IIIf	a	97	120—1	53,00	7,00	—	8,40	$C_{17}H_{26}N_4O_4$	53,39	6,85	—	8,38	77,5
IIIg	c	96	105—6	51,92	6,41	11,82	8,79	$C_{15}H_{21}N_3O_4 \cdot 1/2H_2O$	51,71	6,36	12,06	9,20	192,5
IIIh	a	84	184—6 (dec.)	54,25	7,12	—	8,44	$C_{18}H_{26}N_4O_4S$	54,54	7,12	—	8,09	225,0

In narcotized cats the compounds of group III induce short-term reduction of arterial pressure at doses of 3-10 mg/kg.

When cats are treated in advance with the compounds of group III at doses of 5 and 10 mg/kg, arterial pressure and respiration show reduced response to the subsequent injection of tsitizin, as well as a one third reduction in the duration of its effects; there is also a reduction in the depressive reaction to irritation of the cervical portion of the vagus nerve by an electrical current. The reaction of the cardiovascular system to intravenous injection of acetylcholine is unchanged, but the pressor reaction occurring on injection of adrenalin is somewhat reinforced.

The hydrochlorides of V and VI were investigated in narcotized cats weighing 3-3.5 kg. Narcosis was induced by intraperitoneal injection of a 50-mg/kg dose of barbamil; coughing was induced by irritation of the upper laryngeal nerve (Domenyoz method), with electric impulses (3 V, 40 impulses/sec) applied at a 90° angle; there was a fivefold increase in irritation after 3 seconds with a 2-minute interval between irritations. Coughing was induced up to the time when V and VI were introduced, and then after periods of 3, 15, 30, 60, and 120 minutes. The substances were introduced into the femoral vein in doses of 3, 5, 10, and 15 mg/kg; three to five cats were used for each trial. It was established that at doses of 3 mg/kg, V and VI do not show any influence on the cough reflex; increasing the dose of VI to 5 mg/kg produced a 60-minute depression of the cough reflex in one of the five cats; when VI was administered at a dose of 10 mg/kg we observed in all of the experimental animals an interruption of the cough reflex which lasted for 1.5-2 hours. For narcotized cats, the ED_{50} of VI was found to be 6.8 mg/kg — one third the lethal dose.

Compound V had less cough suppressing activity than VI, which is a closer analog of bitiodin: When V was administered at a dose of 10 mg/kg, the cough reflex was absent in only one of the five cats for a period of 30 minutes, and only at a dose of 15 mg/kg was depression of the cough reflex observed in all the animals, lasting 45-60 minutes. The ED_{50} of V was found to be 11.5 mg/kg — approximately one half the lethal dose.

In toxicity V and VI are similar to bitiodin: The LD_{50} for white mice, by intravenous administration, is 55 mg/kg for bitiodin, 53.5 mg/kg for VI, and 71 mg/kg for V.

At the same time, both compounds are inferior in cough suppressing activity to bitiodin, for which the ED_{50} is equal to 2.8 mg/kg — one fifth the lethal dose.

Thus, for substances which influence the cough and emetic centers, the transition from monocyclic amine derivatives to the quinuclidine analogs does not lead to the same intensification of pharmacological activity that is seen for substances which influence the cholinergic and histaminergic systems; instead, this transition leads to reduction of activity (in the bitiodin analogs) or even to its disappearance (in the sulpiride analogs).

EXPERIMENTAL

Chemistry

General Method for Preparing 2-Methoxy-5-sulfamidobenzoyl Derivatives of 1-Aza- and Diazabicycloalkanes (III). Equimolar quantities (0.01 mole) of azabicyclic amine I and the ethyl es-

ter of 2-methoxy-5-sulfamidobenzoic acid are heated under vacuum (at a residual pressure of 7-20 mm Hg) at a temperature of 120-150° for 4-5 hours. The reaction products are triturated with ether (method a) or with ethanol (method b) and filtered; or they are dissolved in 10 ml water, and the solution is decolorized with carbon, filtered, and evaporated to dryness (method c). Yields, constants, and analytical results for the compounds we synthesized, as well as some of the results of their pharmacological evaluations, are presented in Table 1.

3-Quinuclidinyl-di(2'-thienyl)carbinol (V). A solution of 10 g 3-carbethoxyquinuclidine (IV) in 700 ml ether is added at 0-5° to an ether solution of 2-thienylmagnesium bromide, which has been prepared from 36 g of 2-bromothiophene and 5.3 g magnesium in 150 ml ether. The mixture is allowed to stand for 20 hours at room temperature, and it is then heated at reflux for 6 hours, cooled, and treated with 7% hydrochloric acid. The ether solution is separated, and the acidic aqueous layer is basicified with potassium hydroxide and extracted with chloroform. The residue after evaporation of the chloroform is triturated with ether and recrystallized from a mixture of acetone and alcohol. Yield of V, 6.05 g (36.7%). Found, %: S, 20.8. Calculated for $C_{26}H_{29}NOS_2$, %: S, 21.0.

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

Di-(2'-thienyl)-3-methylenequinuclidine (VI). A solution of 3.8 g 3-quinuclidinyl-di(2'-thienyl)carbinol (V) in 8 ml 85% formic acid is heated at reflux for 30 minutes, after which it is evaporated under vacuum. The residue is basicified with a 50% solution of potassium hydroxide and extracted with benzene. After removal of the benzene, the substance is recrystallized from heptane. Mp 96-97°. Yield of VI, 2.45 g (69%). Found, %: C, 66.54; H, 5.98; S, 22.42. Calculated for $C_{16}H_{17}NS_2$, %: C, 66.85; H, 5.96; S, 22.31.

Hydrochloride, mp 279-281°.

LITERATURE CITED

1. M. D. Mashkovsky and L. N. Jakhontov, Prog. Drug Res., 13, 293 (1969).