AZACYCLOALKANES

XV. RELATION BETWEEN THE STRUCTURE AND NEUROTROPIC ACTIVITY OF 1,4-DIAZABICYCLO[4,m,0]ALKYL DERIVATIVES OF BUTYROPHENONE*

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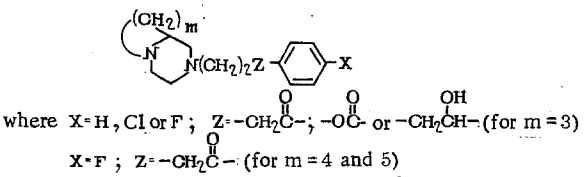
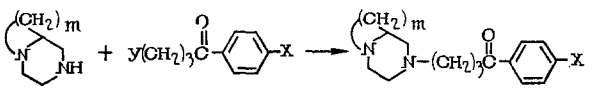
Aminobutyrophenone derivatives have attracted the attention of researchers working in the field of producing new psychotropic agents [1]. Compounds of this type are included among the neurolectics in their pharmacological action, and several of them (haloperidol, haloanisone, etc.) are firmly established in modern clinical psychopharmacology.

Among the possible modifications of the structure of aminobutyrophenones, the preparation of derivatives using various heterocycles as the nitrogen-containing part of the molecule is of great interest. The present work is devoted to synthesizing and studying the neurotropic activity of butyrophenones containing fused piperazine ring systems, viz. 1,4-diazabicyclo[4,m,0] alkanes [2]†, and their structural analogs, with the aim of establishing a relation between their chemical structure and pharmacological activity.



We examined the dependence of the neurotropic activity of these compounds on the following structural factors: a) the structure of the diazabicyclic system; b) the nature of the substituent in the para position of the aromatic ring; and c) the structure of the central part of the molecule.

The aminobutyrophenones (I) were synthesized by alkylating bicyclic amines (II) with γ-halopropyl phenyl ketones (III).



a) m=3; X=F c) m=5, X=F
b) m=4; X=F d) m=3, X=Cl
e) m=3, X=H

The reaction was carried out by heating the components (in a molar ratio of 1:1 or 2:1) in an organic solvent (alcohol, toluene or xylene) or without a solvent. The constants of the compounds I obtained are given in Table 2. The starting ketones III were prepared by Friedel–Crafts acylation of the corresponding aromatic hydrocarbons with γ-halobutyryl chlorides by known methods [4].

*See Khim. Farm. Zh., No. 1, 88 (1976) for communication XIV.

†The other members of this series of compounds are described in the patent literature [3] without any discussion of their pharmacological properties or quoting their constants.

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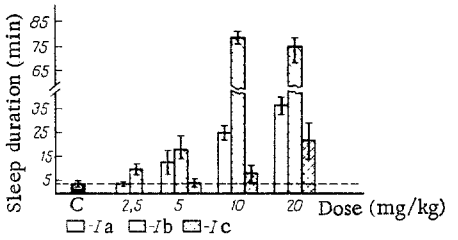


Fig. 1

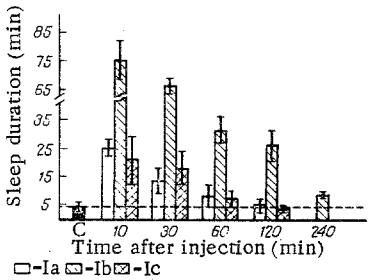


Fig. 2

Fig. 1. Effect of diazabicyclic derivatives of p-flurobutyrophenone on the duration of the narcotic effect of sodium thiopental in white mice.

Fig. 2. Duration of the potentiating effect of diazabicyclic derivatives. Sodium thiopental dose 30 mg/kg.

TABLE 1. Dependence of the Cataleptic Effect of Compounds I on Their Structure

Compound	Dose (mole/kg)	Cataleptic effect
Ia	5.10^{-3}	++++
Ib	5.10^{-3}	++++
Ic	5.10^{-3}	++++
Id	5.10^{-3}	+
	1.10^{-2}	++++
Ie	5.10^{-3}	±
	1.10^{-2}	+

Symbols: (++++) = pronounced catalepsy; (+++) = moderate degree of catalepsy; (++) = mild degree of catalepsy; (+) = isolated signs of catalepsy.

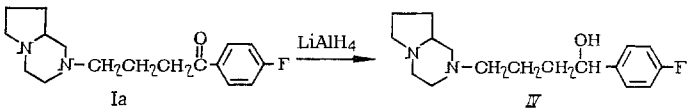
We first studied the relative activity of compounds Ia-Ic as a function of the structure of the diazabicyclic system. The results of investigating the pharmacological properties of these compounds (in the form of their hydrochlorides) using a neuropharmacological screening program showed that they all give a pronounced depressant effect, inducing tranquilization in mice, reducing motor activity, and inducing catalepsy. The characteristic feature of the action of these compounds (when administered intraperitoneally) is the rapidity with which the sedative effect sets in. The neurotropic activity of compounds Ia-Ic was studied in experiments involving potentiation of the narcotic effect of sodium thiopental. The substances were injected intraperitoneally 10 min before administering the sodium thiopental (30 mg/kg iv). The data obtained (Fig. 1) indicate that all three compounds are capable of increasing the duration of the narcotic effect of sodium thiopental, the most active being the diazabicyclodecane derivative Ib (m = 4), which already shows a marked effect at a dose of 2.5 mg/kg. Compound Ia (m = 3) has about half this activity, and Ic (m = 5) shows a marked effect only at a dose of 20 mg/kg. The differences in the structure of these compounds affects not only their activity but also the speed with which the depressant effect sets in and its duration. To study this question in more detail, we administered the substances to mice in a dose of 10 mg/kg and then injected sodium thiopental (30 mg/kg) at different intervals of time. The overall duration of the depressant effect (Fig. 2) was 1 h for compound Ia (m = 3), about 1.5 h for Ic (m = 5), and more than 4 h for Ib (m = 4). Thus, the diazabicyclodecane derivative Ib differs from Ia and Ic not only in its higher activity but also in the considerably longer duration of its action.

A characteristic feature of neuroleptics is their antagonism to amphetamine [5, 6]. These properties are shown in full measure by compounds Ia-Ic. Compound Ia protects against amphetamine-induced hyperactivity in mice (amphetamine dose 10 mg/kg) at doses of 5-10 mg/kg, and Ib is effective at a dose of 1.25-2.5 mg/kg.

Compound Ic is considerably inferior to these, showing an effect only at a dose of 20 mg/kg. The compounds also decrease spontaneous motor activity at doses close to those which are effective in the amphetamine-hyperactivity test. They also have a synchronizing effect on the electroencephalogram of rabbits and inhibit the activating effect of amphetamine.

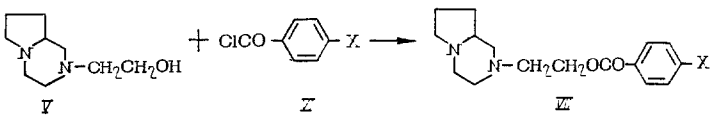
We compared the effect of the nature of the substitutent in the para position of the phenyl nucleus on the neurotropic activity in the case of compounds I (m = 3) containing para-flurophenyl (Ia), para-chlorophenyl (Id) and phenyl (Ie) radicals. The neurotropic effect was characterized by the degree of catalepsy induced (see Table 1). Compounds Ia (X = F) exhibited the greatest effect, while the para-chloro-substituted butyrophenone Id gave a weaker cataleptic effect at twice the dose. It is interesting to note that this effect disappears completely on passing to the analog with an unsubstituted phenyl radical (Ie). These differences in the degree of pharmacological effect are evidently connected with the spatial charge distribution in the butyrophenone molecule as a function of the electron-acceptor properties of the para substitutent.

The neurotropic activity of the compounds of the type under investigation depends significantly on the structure of the central part of the molecule. It has been shown in [7] that among the homologous ω-amino ketones, the butyrophenones have the greatest neurotropic activity, which is why we kept the number of carbon atoms in the central part of the molecule equal to 4 in all the compounds investigated. In order to evaluate the importance of the carbonyl group in the butyrophenone structure of I from the point of view of neurotropic activity, we reduced p-flurophenyl γ-(1,4-diazabicyclo[4,3,0]nonan-4-yl)propyl ketone with lithium aluminum hydride to the corresponding carbinol IV.



The obtained compound had a six times weaker neurotropic effect than Ia, indicating that the carbonyl group plays an important role from the point of view of neurotropic activity.

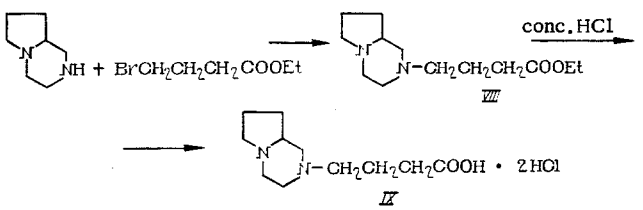
The effect of the structure of the central part of the molecule was also studied for the case of β-(1,4-diazabicyclo[4,3,0]nonanyl)ethyl benzoate esters (VII), in which the α-methylene linkage of compounds I is replaced by an oxygen atom. Compounds VII were prepared by reacting the hydroxyethyl derivative of 1,4-diazabicyclo[4,3,0]nonane (V) with benzoyl or para-fluorobenzoyl chloride (VI):



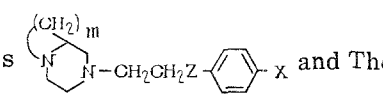
where X = H or F.

The starting amino alcohol V was formed by alkylating 1,4-diazabicyclo[4,3,0]nonane with ethylene oxide in methanol at room temperature. An investigation of the neurotropic properties of esters VII (X = H and F) by testing their potentiation of sodium thiopental narcosis showed that these compounds do not show a significant depressant action.

Since it has been suggested that the neurotropic activity of aminobutyrophenones may be due to their structural similarity to γ-aminobutyric acid (GABA), we synthesized the diazabicyclononane-containing analog of this acid.



Acid hydrolysis of amino ester VII gave the dihydrochloride of γ-(1,4-diazabicyclo[4,3,0]nonan-4-yl)butyric acid (IX). Like GABA itself, compound IX does not display neurotropic properties when administered through the

TABLE 2. 1,4-Diazabicyclo[4,m,0]alkane Derivatives  and Their Dihydrochlorides

Compound	Base									
	yield (%)	boiling point (deg/mm)	n_D^{20}	found (%)			empirical formula	calculated (%)		
				C	H	N		C	H	N
Ie	62,5	155—6/1	1,5438	—	—	—	—	—	—	—
Id	31	168—9,5/1	—	—	—	—	—	—	—	—
Ia	59,3	162—164/1	1,5339	—	—	9,72	$C_{17}H_{23}FN_2O$	—	—	9,65
Ib	50	169—174/0,5	1,5309	—	—	—	—	—	—	—
Ic	62,9	165—167/1,5	1,5352	71,57	8,38	9,06	$C_{19}H_{27}FN_2O$	71,66	8,55	8,8
VII(X=H	58,7	167—168/1	1,5339	69,95	8,11	10,26	$C_{16}H_{22}N_2O_2$	70,03	8,08	10,21
VII(X=F)	38	155—157/1	—	65,37	7,23	9,77	$C_{16}H_{21}FN_2O$	65,75	7,24	9,59
IV	74	173—176/1	1,5299	—	—	—	—	—	—	—

Compound	Dihydrochloride								
	melting point (deg)	found (%)				empirical formula	calculated (%)			
		C	H	N	Cl′		C	H	N	Cl′
Ie	202,5—203,5	59,17	7,86	—	20,39	$C_{17}H_{24}N_2O \cdot 2HCl$	59,13	7,59	—	20,53
Id	213—214,5	53,76	6,62	—	18,52	$C_{17}H_{23}ClN_2O \cdot 2HCl$*	53,76	6,64	—	18,67
Ia	182—184†	53,8	6,95	7,39	18,36	$C_{17}H_{23}FN_2O \cdot 2HCl \cdot H_2O$	53,56	7,14	7,35	18,60
Ib	230—231	—	—	7,57	17,92	$C_{18}H_{25}FN_2O \cdot 2HCl \cdot H_2O$‡	—	—	7,09	17,93
Ic	222,5—224	—	—	—	17,41	$C_{19}H_{27}FN_2O \cdot 2HCl \cdot H_2O$	—	—	—	17,32
VII(X=H)	151,5—153	—	—	—	19,07	$C_{16}H_{22}N_2O_2 \cdot 2HCl \cdot H_2O$	—	—	—	19,41
VII(X=F)	215—217	—	—	—	18,73	$C_{16}H_{21}FN_2O_2 \cdot 2HCl \cdot H_2O$	—	—	—	18,50
IV	225—227	55,96	7,56	—	19,36	$C_{17}H_{25}FN_2O \cdot 2HCl$	55,89	7,45	—	19,41

*Found: 27.92% total Cl. Calculated: 28.02% total Cl.
†Literature data: mp 180-181°.
‡Found: 5.00% F. Calculated: 5.04% F.

usual routes; this is evidently connected with the low permeability of the hemato-encephalic barrier for these substances.

Thus, of all the compounds that we have investigated, the butyrophenones containing 1,4-diazabicyclic systems as γ-substituent are of greatest interest for the synthesis of potential psychotropic agents. One of these compounds, viz. p-fluorophenyl γ-(1,4-diazabicyclo[4,3,0]nonan-4-yl)propyl ketone, has successfully passed pharmacological and clinical tests and has been authorized for medical use under the name "azabutyrone".

EXPERIMENTAL

The constants, yields and analysis data of the compounds prepared are given in Table 2. The dihydrochlorides of all the compounds were prepared by mixing together ether solutions of the base and hydrogen chloride.

Phenyl γ-(1,4-Diazabicyclo[4,3,0]nonan-4-yl)propyl Ketone (Ie). A mixture of 0.01 mole of γ-chloropropyl phenyl ketone and 0.02 mole of 1,4-diazabicyclo[4,3,0]nonane was heated at 100° for 30 min, cooled, treated with 15 ml of water, extracted with ether, the ether evaporated off, and the residue distilled in vacuo.

p-Chlorophenyl γ-(1,4-Diazabicyclo[4,3,0]nonan-4-yl)propyl Ketone (Id). A solution of 0.01 mole of p-chlorophenyl γ-chloropropyl ketone and 0.02 mole of 1,4-diazabicyclo[4,3,0]nonane in 40 ml of absolute alcohol was boiled for 8 h in the presence of a catalytic amount of potassium iodide. The alcohol was evaporated off, the residue treated with 10 ml of water, extracted with ether, the ether evaporated off, and the product distilled in vacuo.

p-Fluorophenyl γ-(1,4-Diazabicyclo[4,4,0]decan-4-yl)propyl Ketone (Ib). A solution of equimolar amounts of 1,4-diazabicyclo[4,4,0]decane and p-fluorophenyl γ-chloropropyl ketone in dry toluene was boiled for 16 h, cooled, adjusted to pH 1.0 with 7% hydrochloric acid solution, and the aqueous phase separated, alkalized with 10% sodium hydroxide solution, and extracted with ether. The ether was evaporated off and the residue distilled in vacuo.

p-Fluorophenyl γ-(1,4-Diazabicyclo[4,5,0]undecan-4-yl)propyl Ketone (Ic). A mixture of 0.04 mole of 1,4-diazabicyclo[4,5,0]undecane and 0.02 mole of p-fluorophenyl γ-bromopropyl ketone was heated at 100° for

0.5 h, cooled, treated with 20 ml of water, extracted with ether, the ether evaporated off, and the residue distilled in vacuo. p-Flurophenyl γ-(1,4-diazabicyclo[4,3,0]-nonan-4-yl)propyl ketone (Ia) was prepared analogously from 1,4-diazabicyclo[4,3,0]nonane and p-fluorophenyl γ-bromopropyl ketone.

p-Fluorophenyl γ-(1,4-Diazabicyclo[4,3,0]nonan-4-yl)propyl Carbinol (IV). A solution of 0.01 mole of p-fluorophenyl γ-(1,4-diazabicyclo[4,3,0]nonan-4-yl)propyl ketone in 20 ml of absolute ether was added dropwide to a suspension of 0.05 mole of lithium aluminum hydride in 50 ml of absolute ether. The mixture was stirred and boiled for 10 h and, on cooling, decomposed by successive addition of 2.5 ml of water, 1.5 ml of of 20% sodium hydroxide solution, 7.5 ml of water, and 17 ml of 20% sodium hydroxide solution. The reaction mixture was treated with 30 ml of ether, boiled for 30 min, and the ether solution decanted and dried with magnesium sulfate. The ether was evaporated off and the residue distilled in vacuo.

N-Benzoyloxyethyl-1,4-diazabicyclo[4,3,0]nonane (VII, X = H). A solution of 0.01 mole of N-(β-hydroxyethyl)-1,4-diazabicyclo[4,3,0]nonane (V) in 30 ml of dry chloroform was treated dropwise with 0.02 mole of benzoyl chloride while cooling and stirring. The mixture was kept at room temperature for 1 h, boiled for 1 h, and evaporated to dryness. The residue was treated with 20 ml of water, acidified to pH 1.0 with concentrated hydrochloric acid, extracted with ether, and the aqueous phase treated with 10% sodium hydroxide solution to pH 9.0-10.0, extracted with ether, and the ether solution dried with magnesium sulfate. The ether was evaporated off and the residue distilled in vacuo. N-(p-Fluorobenzoyloxyethyl)-1,4-diazabicyclo[4,3,0]nonane (VII, X = F) was prepared analogously from equimolar amounts of V and p-fluorobenzoyl chloride.

γ-(1,4-Diazabicyclo[4,3,0]nonan-4-yl)butyric Acid Dihydrochloride (IX). A mixture of 4 moles of amino ester VIII* and 5 ml of concentrated hydrochloric acid was kept at room temperature for 48 h, evaporated to dryness, and evaporated with water and then with benzene. After crystallizing the residue, it was washed with acetone. Yield 0.8 g (66.5%), mp 203-204°. Found, %: Cl 23.57. $C_{11}H_{20}N_2O_2 \cdot 2HCl \cdot H_2O$. Calculated, %: Cl 23.39.

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*Prepared from 1,4-diazabicyclo[4,3,0]nonane and ethyl γ-bromobutyrate.