HYDROCHLORIDES OF γ-HEXAMETHYLENEIMINOPROPYL ESTERS OF α-ALKOXY-DIPHENYLACETIC AND α-PHENYLCYCLOHEXYLGLYCOLIC ACIDS AND THEIR PHARMACOLOGICAL PROPERTIES

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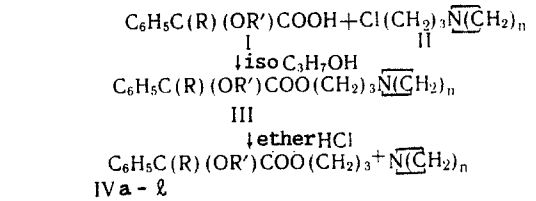
UDC 615.217.34.012.1

During investigations that were carried out earlier it was found that hydrochlorides of γ-diethylaminopropyl esters of α-alkoxydiphenylacetic acid are distinct cholinolytics [6]. They differ from their analogs – β-diethylaminoethyl derivatives – by strongly expressed nicotinolytic properties and considerable influence on the CNS.

With the purpose of investigating the influence of a more rigid conformation of the amino part of the molecule on the observed properties, we have synthesized the hydrochlorides of γ-hexamethyleneiminopropyl esters of α-alkoxydiphenylacetic and α-phenylcyclohexylglycolic acids and also, for comparison study, the piperidine and pyrrolidine derivatives:



R=C_6H_5 (IVa-i), C_6H_{11} (IVj-ℓ) R'=H (IVa, j-ℓ), CH_3 (IVb), C_2H_5 (IVc), C_3H_7 (IVd) iso-C_3H_7 (IVe), C_4H_9 (IVf) iso-C_4H_9 (IVg), C_5H_{11} (IVh) iso-C_5H_{11} (IVi); n=6 (IVa–i, ℓ), 4 (IVj), 5 (IVk)

α-Alkoxydiphenylacetic acids (R=C_6H_5) were synthesized from benzilic acid by an earlier described method [5].

Chromatographic study (TLC and GLC) of the reaction products with the example of the reaction of benzilic acid (V) with ethyl alcohol in the presence of sulfuric acid showed that in addition to the main product, the ethyl ester of benzilic acid (VI), there is also formed another product (VII) with a boiling point close to the boiling point of compound VI. Separation of the mixture by usual distillation under vacuum was unsuccessful. By-product VII does not react with thionyl chloride and distils under vacuum together with the ethyl ester of α-chlorodiphenylacetic acid (VIII). With respect to chromatographic mobility it coincides with the ethyl ester of α-ethoxydiphenylacetic acid, which was prepared by treating chloro derivative VIII with sodium ethylate.

We have studied the influence of the ratio of the reagents (sulfuric acid and ethanol) on the ratio of products VI and VII. We have found that in the case of a twofold excess of sulfuric acid and ethanol the yield of by-product VII is increased from 22.4 to 30%, and in the case of only a twofold excess of sulfuric acid it amounts to 42.5%.

Thus, formation of the ethyl ester of α-ethoxydiphenylacetic acid VII in the esterification of the carboxyl group of benzilic acid was found. By filtration from an aqueous solution and subsequent recrystallization the ester of α-chlorodiphenylacetic acid VIII can be freed almost completely from compound VII, which, of course, lowers the yield of final product.

A. L. Mndzhoyan Institute of Fine Organic Chemistry, Academy of Sciences of the Armenian SSR, Erevan. Translated from Khimiko-farmatsevticheskii Zhurnal, Vol. 24, No. 3, pp. 17-19, March, 1990. Original article submitted March 29, 1989.

 0091-150X/90/2403-0170 $12.50 © 1990 Plenum Publishing Corporation

TABLE 1. Hydrochlorides of γ-Cycloalkyliminopropyl Esters of α-Alkoxydiphenylacetic and α-Phenylcyclohexylglycolic Acids (IVa-ℓ)

Compound	Yield, %	mp, °C	F_f(A)	Empirical formula
IV a	59,0	116—117	0,63	$C_{23}H_{30}ClNO_3$
IV b	74,0	123—124	0,49	$C_{24}H_{32}ClNO_3$
IV c	59,2	138—139	0,51	$C_{25}H_{34}ClNO_3$
IV d	54,6	113—114	0,52	$C_{26}H_{36}ClNO_3$
IV e	56,8	109—110	0,51	$C_{26}H_{36}ClNO_3$
IV f	52,7	138—139	0,53	$C_{27}H_{38}ClNO_3$
IV g	54,5	103—104	0,54	$C_{27}H_{38}ClNO_3$
IV h	49,0	145—146	0,55	$C_{28}H_{40}ClNO_3$
IV i	50,7	128—129	0,56	$C_{28}H_{40}ClNO_3$
IV j	61,4	182—183	0,58	$C_{28}H_{32}ClNO_3$
IV k	51,2	192—193	0,62	$C_{22}H_{34}ClNO_3$
IV ℓ	45,4	176—177	0,65	$C_{23}H_{36}ClNO_3$

The synthesis of phenylcyclohexylglycolic acid was carried out by reacting with the ethyl ester of benzoylformic acid [3] with cyclohexylmagnesium bromide and subsequent hydrolysis of the ethyl ester of α-phenylcyclohexylglycolic acid [8] in an aqueous methanolic solution of sodium hydroxide [10].

Compounds II were prepared by reacting 1-bromo-3-chloropropane with the appropriate secondary amine [9].

By heating compounds I and II in isopropanol we synthesized aminoesters III, the hydrochlorides of which (IV) were prepared by reaction with an ethereal solution of hydrochloric acid (Table 1).

EXPERIMENTAL (CHEMICAL)

Melting points were determined on a Boetius melting microscope (GDR). IR spectra were taken in paraffin oil and chloroform on a UR-20 spectrometer (GDR). Mass spectra were recorded on an MX-1320 instrument with direct introduction of the sample in the ion source; electron ionization energy 65-70 eV.

TLC of hydrochlorides IV and acid I was carried out on a fixed layer of macroporous silica gel—gypsum with the eluents: A) n-butanol—ethanol—acetic acid—water 8:2:1:3 and B) ethanol—water—ammonia 80:15:5, respectively, with visualization with Dragendorff's reagent (for system A) and bromcresol blue (for system B). TLC of compounds VI-VIII was carried out on Silufol plates (Czechoslovakia) with the eluent hexane—diethyl ether 4:1; spots were visualized with a 5% alcoholic solution of phosphomolybdic acid.

GLC was carried out on a Chrom-4 instrument (Czechoslovakia) equipped with a flame ionization detector and a column (2500 × 3 mm) with 5% silicone XE-60 on Chromaton N-AW-DMCS (0.16-0.20 mm) under isothermic conditions (200°C) and with temperature programming from 170 to 235°C (5°C/min). The temperature of the evaporator was 240°C and the rate of the carrier gas (nitrogen) 80 ml/min. Quantitative analysis was carried out with the method of internal standardization. Assignment of the peaks of the ethyl esters of benzilic acid and α-ethoxydiphenylacetic acid was realized by comparing with pure samples, which were isolated from the mixtures by means of column chromatography and identified by means of IR and mass spectroscopy.

Column Chromatography. Separation of the mixture of the ethyl esters of benzilic and α-ethoxydiphenylacetic acid was carried out on a column of Florisil (0.08-0.15 mm; Serva). Elution was done with a mixture of hexane and diethyl ether (4:1) and the elution was monitored with TLC. IR spectrum of VI, ν, cm^{-1}: 3500 (tert-OH), 3000-3070 (arom.), 2860-2990 (C_2H_5), 1720 (C=O ester). Mass spectrum, m/z: 256 (M^+). IR spectrum of VII, ν, cm^{-1}: 3030-3090 (arom.), 2890-2980 (C_2H_5), 1750 (C=O ester). Mass spectrum, m/z: 284 (M^+).

Hydrochlorides of γ-Cycloalkylaminopropyl Esters of α-Alkoxydiphenylacetic and α-Phenylcyclohexylglycolic Acids (IVa-ℓ). A mixture of 0.04 mole of compound I and 0.046

TABLE 2. Parameters of the Spasmolytic and Local Anesthetic Activities of the Hydrochlorides of Aminoesters IVa-ℓ

Compound	Concentrations lowering by 50% the acetylcholine contracture the rectus of frog bellies, g/ml	Concentrations lowering by 50% the acetylcholine contraction of isolated pieces of cat intestines, g/ml	Concentrations lowering by 50% the value of the contracture of isolated pieces of rabbit intestines evoked by barium chloride, g/ml	Value of the hypotensive effect (in mm Hg) evoked by administering the compound at a dose of 2 mg/kg	Local anesthetic activity, % (M ± m)	Doses lowering by 50% the pressor effect of subecholine, mg/kg	Doses lowering by 50% the depressive effect of acetylcholine, mg/kg
IV.a	$2 \cdot 10^{-6}$	$5{,}8 \cdot 10^{-6}$	$2 \cdot 10^{-6}$	18	55,4±4,2	2,0	—
IV.b	$2{,}5 \cdot 10^{-6}$	$9 \cdot 10^{-6}$	$2{,}2 \cdot 10^{-6}$	32	53,2±4,3	2,0	—
IV.c	$2 \cdot 10^{-6}$	$2{,}7 \cdot 10^{-7}$	$1{,}5 \cdot 10^{-6}$	22,5	41,9±2,1	2,3	1,75
IV.d	$1 \cdot 10^{-5}$	$1{,}2 \cdot 10^{-6}$	$9 \cdot 10^{-5}$	14	35,3±4,8	2,2	2,4
IV.e	$3 \cdot 10^{-6}$	$5{,}6 \cdot 10^{-8}$	$3 \cdot 10^{-6}$	31	25,4±2,55	2,0	1,6
IV.f	$2{,}5 \cdot 10^{-6}$	$3{,}2 \cdot 10^{-6}$	$5 \cdot 10^{-6}$	30,5	40,4±2,54	1,7	—
IV.g	$2 \cdot 10^{-5}$	$7{,}2 \cdot 10^{-7}$	$1{,}2 \cdot 10^{-6}$	15	25,4±1,35	1,7	1,75
IV.h	$2{,}5 \cdot 10^{-6}$	$6 \cdot 10^{-6}$	$2{,}5 \cdot 10^{-6}$	12,5	38,9±1,9	1,9	3,5
IV.i	$2{,}5 \cdot 10^{-6}$	$1 \cdot 10^{-6}$	$2{,}8 \cdot 10^{-6}$	18	40,6±2,9	1,8	3,4
IV.j	$4 \cdot 10^{-6}$	$8 \cdot 10^{-9}$	$3 \cdot 10^{-6}$	17,5	68,6±4,6	2,1	1,7
IV.k	$5 \cdot 10^{-6}$	$9{,}8 \cdot 10^{-9}$	$5 \cdot 10^{-6}$	30	47,7±2,91	2,0	1,3
IV.ℓ	$5 \cdot 10^{-6}$	$9{,}6 \cdot 10^{-9}$	$8 \cdot 10^{-6}$	15	34,0±3,1	2,4	3,0
Papaverine (hydrochloride)	—	—	$1{,}5 \cdot 10^{-5}$	45	—	—	—
Novocain	—	—	—	—	73,0±0,1	—	—

mole of freshly distilled amine II in 50 ml of isopropyl alcohol was refluxed for 14-15 h. The solvent was evaporated, the residue was treated with a saturated solution of potassium carbonate, and extracted with ether. The ethereal layer was dried over sodium sulfate and filtered. Hydrochlorides IV (see Table 1) were prepared by reaction with an ethereal solution of hydrochloric acid. IR spectra of IV, ν, cm^{-1}: 1740-1760 (C=O), 1500-1600 (C_6H_5), 2400-2900 ($-N^+-Cl^-$).

Data of elemental analyses were in agreement with calculated values.

EXPERIMENTAL (PHARMACOLOGICAL)

Hydrochlorides IV were tested for cholinolytic, spasmolytic, anticonvulsive, anticholinesterase, local anesthetic, and analgesic activities. The peripheral cholinolytic activity was studied in experiments with isolated organs and with the intact organism. The criterion for cholinolytic activity was the concentration of the compound that lowered by 50% the value of the acetylcholine contractures of rectus of frog bellies and isolated pieces of ileum of cats.

In experiments with narcotized cats the degree of cholinolytic and ganglioblocking activities was judged by the doses of the compound that lowered the depressive effect of acetylcholine and by the doses that lowered (weakened) the pressor effect of the nicotine-like preparation subecholine.

The spasmolytic activity was determined by the influence of the compounds on the contraction of isolated pieces of rabbit intestine evoked by barium chloride and by the degree of the hypotensive effect in cats [4].

The anticholinesterase activity was studied in vitro with the potentiometric titration method [2]. We determined the concentrations of the compounds that inhibit the activity of cholinesterase of human erythrocytes by 50% ($I_{50}M$).

The central cholinolytic activity was studied with the models of nicotine convulsions and arecoline tremor in sick mice. As convulsive models we also used electroshock and corazol convulsions [12, 13].

The local anesthetic activity of the compounds with regard to conduction anesthesia was studied with isolated frog nerves [1]. Surface-anesthetic activity was studied with the cornea of rabbit eyes; the intensity of the anesthesia was determined according to Reigner's method [11].

The central analgesic action and the antimorphine activity of compounds IV was studied with the model of mechanical irritation of rat tails [7]. The compound was administered subcutaneously at a dose of 10 mg/kg. Altogether we used 280 mice, 20 rats, 35 rabbits, 60 frogs, and 30 cats.

During the investigation of the anticonvulsive properties of compounds IV it was found that on intraperitoneal administration at a dose of 50-60 mg/kg the compounds somewhat weakened the nicotinic convulsions and did not have influence on arecoline tremor. Further increasing of the doses to obtain complete prevention of convulsions proved to be impossible because toxic effects were brought about (toxic doses 75-150 mg/kg). At the doses mentioned above the compounds did not change the nature of the convulsions evoked by electric stimulation, but to some degree weakened the intensity of corazol convulsions. In that case the activity was increased with increasing the size of the alkoxy group at the α-position. The highest activity was shown by compound IVg.

The results obtained in the study of the spasmolytic activity showed that all the compounds studied in experiments with isolated organs have high cholinolytic activity and distinct myotropic activity that is not inferior to that of papaverine (Table 2).

The highest hypotensive activity is found in compounds IVb and e, which lower the arterial pressure by 32 mm Hg.

With regard to the ganglioblocking activity (according to the lowering of the pressor effect of subecholine), the highest activity is shown by compounds IVf-i, containing at the α-position a butyl, isobutyl, amyl, and isoamyl radical, respectively. They lower the pressor effect of subecholine by 50% in the dose range of 1.7-1.8 mg/kg (see Table 2).

Typical of compounds IV are anticholinesterase properties, however, their activity is rather low; their $I_{50}M$ values are in the range 1.8×10^{-4}-1.3×10^{-5}.

It was found that only compounds IVa and IVj have a weak local anesthetic activity (55 and 68%, respectively).

All the compounds studied did not show either analgesic or antimorphine activity.

Thus, hydrochlorides IVa-ℓ cause central and peripheral n-cholinolytic action and also a weakly expressed anticorazol action. With regard to direct myotropic action most of them are not inferior to papaverine.

Only the local anesthetic activity of compound IVj was similar to the action of Novocain.

The results of the experiments that were carried out indicate that creation of a more rigid conformation in the amino part of the molecule of aminoesters of α-alkoxydiphenylacetic acids leads to lowering of the cholinolytic activity both in the case of convulsions evoked by nicotine and in the case of arecoline tremor.

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