STUDIES ON A SERIES OF CYCLOBUTANEDI-CARBOXYLIC ACIDS VII. SYNTHESIS AND CURARE-LIKE ACTIVITY OF BISQUATERNARY SALTS OF ALKYLAMINO ESTERS OF p,p'-SUBSTITUTED α -TRUXILLIC ACIDS

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A number of active muscle relaxants have been found among the bisquaternary salts of alkylamino derivatives of the stereoisomeric diphenylcyclobutanedicarboxylic acids of general formula I [1-4]. Certain of the studied compounds have been referred to clinical trials; and, as a result of these, the most effective compounds, Cyclobutonium (IIa) and Anatruxonium (IIb), were selected and recommended for use in anesthetic practice. These compounds proved to be highly active and weakly toxic curare-like substances of medium duration of action and resembled typical nondepolarizing muscle relaxants in the mechanism of action [5].



All the compounds of I previously studied by us were related to derivatives of diphenylcyclobutanedicarboxylic acids unsubstituted in the aromatic rings. Therefore, it was of interest to synthesize and test (as dimethiodides*) analogs of one of the most active compounds, IIb, containing in the phenyl rings substituents differing in their electronic nature, namely p, p'-dinitro, p,p'-dimethoxy, and p,p'-dihydroxy groups (IIc-e). The last of these compounds (IIe) is also of interest in that it is closest in structure to the natural alkaloid thesine [6, 7], the curare-like activity of which [8] was the basis for the synthesis of the whole group of compounds I [3].

*Although IIb is an ethiodide we synthesized and tested the corresponding methiodides since in activity and nature of action they are not different from the ethiodides [3] and, at the same time, they are considerably more readily obtained in the crystalline form.

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The route via p,p'-dinitro- α -truxillic acid (IV) [7] (see scheme below) could have been the simplest for preparing the p,p'-dinitro analog of IIb (IIc).



However, all attempts to convert compound IV into the diacid chloride (V) by the action of thionyl chloride or phosphorus pentachloride failed; furthermore, chlorination of the acid occurred. Also transesterification of the dimethyl ester (VI) did not take place; the original substance was recovered unchanged on heating the ester with γ -(N-piperidyl)propanol in the presence of alcoholate. The synthesis was accomplished starting from the di-[γ -(N-piperidyl)propyl] ester of α -truxillic acid (VII) [9]. This substance forms a well crystallized nitric acid salt (VIII), the nitration of which leads to the p,p'-dinitro ester (IX); the latter is converted into the required product (IIc) on reaction with methyl iodide. The position of the nitro groups and the absence of stereoisomerization during the nitration are demonstrated by the fact that the acid IV is formed in high yield on saponification of the dinitro ester (IX); the acid was identified by conversion into the dimethyl ester (VI).

The synthesis of the p,p'-dimethoxy analog (IId) was carried out without difficulty from p,p'-dimethoxy- α -truxillic acid (X) [6] by successive conversion into the diacid chloride (XI), the di-[γ -(N-piperidyl)propyl] ester (XII), and the dimethiodide (IId).

The dimethyl ester of thesinic acid (XIII) [6] was selected as starting substance for the synthesis of the p,p'-dihydroxy derivative (IIe).

In order to protect the p-hydroxy groups, this compound was converted by the action of benzyl chloride into the dimethyl ester of p,p'-dibenzyloxythesinic acid (XIV), alkaline hydrolysis of this led to p,p'-dibenzyloxythesinic acid (XV). The latter was converted via the diacid chloride (XVI) into the corresponding di-[γ -(N-piperidyl)propyl] ester (XVII) from which the benzyl groups were removed by hydrogenation in the presence of palladium on charcoal. The dialkamino ester (XVIII) obtained by such means was converted into the dimethiodide (IIe) by the action of methyl iodide.

It was shown in the pharmacological study of compounds IIb-e that they all possessed an expressed curare-like activity. This gives rise to a depression of the neuromuscular transmission and a relaxation of the muscle until complete arrest of respiration. Compound IIb (X=H) was the most effective curare-like substance. Substitution of X by a nitro, methoxy, or hydroxy group leads to a reduction of the myoparalytic activity (see Table 1). Hence, the maximum approach to the structure of the biologically active natural compound selected as a model, the alkaloid thesine (which contains the same acidic fragment as in compound IIe), is not optimal in this case. TABLE 1. Curare-like Activity of Methiodides of Di-[γ -(N-piperidyl)propyl] Esters of p,p'-Substituted α -Truxillic Acids.

Com -	x	Blocking action on transmission of excitation from sciatic nerve to gastro- <u>cnemius muscle</u> mg/kg in	Curare-like ac- tivity according to the ability to evoke the symptom of inclination of the head in rabbits travenously
II a	H	0,07-0,1	0,02-0,025
II b	NO2	0,12-0,14	0,075-0,08
II c	CH3O	0,15-0,18	0,05-0,06
II d	OH	0,15-0,18	-

According to the mechanism of action the compounds tested are related to the nondepolarizing substances. In experiments on chicks they all caused flaccid paralysis. Furthermore, the antagonism with neostigime noted in the experiments on cats from the record of the nerve impulse transmission from the sciatic nerve to the gastrocnemius confirms this.

EXPERIMENTAL

Nitric Acid Salt of Di-[γ -(N-piperidyl)propyl] Ester of α -Truxillic Acid (VIII). A 20% solution of hydrochloric acid was added with stirring to a mixture of 5.5 g of VII [1] in 200 ml of water until the precipitate dissolved completely. To the obtained solution was added 3.4 ml of 60% nitric acid, and the mixture was left to crystallize for 3 h. The crystals of nitric

acid salt which separated were filtered off, washed with 50 ml of water, and dried in vacuum. The yield was 5.58 g of a substance with mp 183-184°C (decomp.). Found %: N 8.31; 8.29. $C_{34}H_{46}N_2O_4 \cdot 2HNO_3$. Calculated %: N 8.32.

 $Di-[\gamma-(N-piperidyl)propyl]$ Ester of p,p'-Dinitro - α -truxillic Acid (IX). While stirring thoroughly, 6 g of VIII was added slowly to 30 ml of nitric acid (sp. gr 1.5) maintained at 35-37°. Then the reaction mixture was stirred for 2 h, decomposed with ice water, made basic with 25% ammonia solution, and extracted with ethyl acetate. The extract was dried with magnesium sulfate, the ethyl acetate was distilled off in vacuum, the mixture of nitro products (4.5 g) which remained was treated with 30 ml of ether, and the precipitate was filtered off. This gave 1.65 g (30.2%) of a substance with mp 131.5-132° (from methanol). Found %: C 64.25; 63.85; H 7.06; 7.04; N 8.52; 8.90. C₃₄H₄₄N₄O₈. Calculated %: C 64.13; H 6.96; N 8.80.

Dimethiodide of Di-[γ -(N-piperidyl)propyl] Ester of p,p'-Dinitro- α -truxillic Acid (IIc). A mixture of 0.4 g of IX, 5 ml of methanol, and 0.7 ml of methyl iodide was heated with boiling on a water bath for 3 h until it was no longer alkaline. After evaporation of the methanol, the residue crystallized. The yield was 0.39 g of crystals with mp 257-259° (from 50% alcohol). The substance was difficultly soluble in water, al-cohol, and other solvents. Found %: I⁻ 27.71; 27.62. C₃₆H₅₀I₂N₄O₈. Calculated %: I⁻ 27.57.

<u>Hydrolysis of Di-[γ -(N-piperidyl)propyl]</u> Ester of p,p'-Dinitro- α -truxillic Acid (IX). A solution of 0.5 g of IIc in 10 ml of 20% hydrochloric acid was heated to reflux for 2 h. After cooling, the precipitate of IV which separated was filtered off, washed with water, and dried in a vacuum desiccator. This gave 0.24 g of the acid with mp 293-295°. The yield was 80%. According to the literature data [7] the mp is 296-298°.

To a solution of 0.19 g of the obtained sample of IV in 2 ml of 0.5 N sodium hydroxide solution was added 0.09 ml of dimethyl sulfate with stirring. The solution clouded after heating to 50° and in 5 min crystals of the dimethyl ester VI separated. The reaction mixture was made basic with 0.5 N sodium hydroxide solution, the precipitate was filtered off, washed with water, and dried in vacuum. This gave 0.17 g (80%) of VI with mp 223-224°. According to the literature data [7] the mp is 226°.

A mixture of the obtained substance with an authentic sample of VI did not show a melting point depression.

Diacid Chloride of p,p'-Dimethoxy- α -truxillic Acid (XI). A mixture of 7 ml of dichloroethane, 1,2 g of X [6], 1.7 ml of thionyl chloride, and 0.02 ml of pyridine was heated to 70°. The reaction had finished in 1 h and complete solution of the precipitate had occurred. The dichloroethane and the excess of thionyl chloride, were distilled off in vacuum, 7 ml of dichloroethane was added to the residue and the solution was left for 12-15 h at -15°. The crystals which formed were filtered off and washed twice with cold dichloroethane. After drying in a vacuum desiccator 1.1 g (76.9%) of a substance with mp 149-150° was obtained. Found %: Cl 17.75; 17.65. C₂₀H₁₈Cl₂O₄. Calculated %: Cl 18.03.

<u>Di-[γ -(N-piperidyl)propyl]</u> Ester of p,p'-Dimethoxy- α -truxillic Acid (XII). A solution of 1, 1 g of XI in 7 ml of dichloroethane was added with stirring to a cooled solution of 1 g of γ -(N-piperidyl)propanol in 5 ml of dichloroethane and the reaction mixture was left for 15 h at room temperature. Then 5 ml of water was added with the temperature not exceeding 10° and the mixture was stirred for 10 min, the aqueous layer was separated, the dichloroethane layer was extracted with 5% sulfuric acid (3 times by 2.5 ml) and then once with 2.5 ml of water. The combined extract was made basic with 25% ammonia solution until pH 9. The base which separated as a viscous oil crystallized on cooling. The precipitate was filtered off, washed with water, and dried in vacuum. This gave 1.1 g (64.7%) of a substance with mp 120-121° (from absolute ether). Found %: C 70.93; 70.89; H 8.16, 8.00; N 4.67, 4.70. $C_{36}H_{50}N_2O_6$. Calculated %: C 71.22; H 8.30; N 4.61.

<u>Dimethiodide of Di-[γ -(N-piperidyl)propyl]</u> Ester of p,p'-Dimethoxy- α -truxillic Acid (IId). A mixture of 0.4 g of XII, 5 ml of methanol, and 0.7 ml of methyl iodide was heated for 2 h on a water bath at 60-80° until no longer alkaline. The residue after distilling off the methanol crystallized on triturating in absolute acetone. The precipitate was filtered off, washed with acetone, and dried. This gave 0.55 g (94.6%) of a substance with mp 253°. Found %: I⁻ 28.77, 28.49. C₃₈H₅₆I₂N₂O₆. Calculated %: I⁻ 28.49.

Dimethyl Ester of p,p'-Dibenzyloxy- α -truxillic Acid (XIV). A mixture of 7.2 g of XIII [6] and 5 ml of benzyl chloride was added with stirring to a solution of 2.4 g of potassium hydroxide in 200 ml of 50% alcohol. The reaction mixture was stirred while boiling for 7 h, on cooling it was basified to pH 9.5 with 20% potassium hydroxide solution and stirred for a further hour. The precipitate was filtered off, washed with water, and dried. This gave 6.9 g (63.8%) of a substance with mp 155° (from alcohol). Found %: C 76.39, 76.17; H 6.06, 6.00. $C_{34}H_{32}O_{6}$. Calculated %: C 76.08; H 6.01.

<u>p.p'-Dibenzyloxy- α -truxillic Acid (XV)</u>. To a solution of 32 g of potassium hydroxide in 320 ml of 50% alcohol was added 5.4 g of XIV and the mixture was boiled with stirring for 6 h. After cooling, the solution was acidified with 20% sulfuric acid solution, the precipitate was filtered off, washed with water, and dried. This gave 4.7 g (92.5%) of a substance with mp 263-265°. Found %: C 75.00, 74.95; H 5.57, 5.63. C₃₂H₂₈O₆. Calculated %: C 75.60; H 5.51.

Diacid Chloride of p,p'-Dibenzyloxy- α -truxillic Acid (XVI). A mixture of 2 g of XV, 30 ml of dichloroethane, and 2 drops of dimethylformamide was heated until the precipitate dissolved. The solution was filtered and left for 10 h at 5-10°. The crystals which separated were washed with ether and dried in vacuum. This gave 1.36 g (65.4%) of a substance with mp 199-200° (from dichloroethane). Found %: Cl 13.17, 13.36. $C_{32}H_{26}Cl_2O_4$. Calculated %: Cl 13.02.

 $\frac{\text{Di}-[\gamma-(\text{N-piperidyl})\text{propyl}] \text{ Ester of p,p'-Dibenzyloxy-}\alpha-\text{truxillic Acid (XVII)}. \text{ To a cooled solution of 0.86 g of }\gamma-(\text{N-piperidyl})\text{propanol in 40 ml of dichloroethane was added 1,31 g of XVI at a temperature not exceeding 10°. The reaction mixture was stirred for a further 2 h and left for 15 h at room temperature, the dichloroethane was evaporated off and the residue triturated with ether. The crystals were filtered off, washed with ether, treated with 10% ammonia solution, and then with water. This gave 1.2 g (65.9%) of a substance with mp 135-137° (from alcohol). Found %: C 75.92; 75.41; H 7.75, 7.69; N 3.90 3.89. C₄₈H₅₈N₂O₆ Calculated %: C 76.00; H 7.65; N 3.69.$

The dimethiodide, mp 233-235° (from alcohol) was difficultly soluble in water, alcohol, and other solvents. Found %: I⁻ 24.83, 24.95. $C_{50}H_{64}I_2N_2O_{6*}$ Calculated %: I⁻ 24.38.

 $\frac{\text{Di}-[\gamma-(\text{N-piperidyl})\text{propyl}] \text{ Ester of p,p'-Dihydroxy}-\alpha-\text{truxillic Acid (XVIII)}. A mixture of 0.7 g of XVII, 30 ml of absolute alcohol, and 0.3 g of 5% Pd on charcoal was shaken in an atmosphere of hydrogen for 2 h. The solution was filtered from catalyst and evaporated to a volume of 5 ml; the crystals which separated were washed with absolute alcohol. This gave 0.47 g (98.1%) of a substance with mp 199-201° (from alcohol): it dissolved in dilute acids and caustic alkali and was insoluble in ammonia. Found %: C 70.43, 70.52; H 7.97, 8.17; N 5.04, 4.87. C₃₄H₄₆N₂O₆. Calculated %: C 70.56, H 8.01; N 4.83.$

Dimethiodide of $Di-[\gamma-(N-piperidyl)propyl]$ Ester of p,p'-Dihydroxy- α -truxillic Acid (IIe). A mixture of 0.4 g of XVIII, 10 ml of methanol, and 1 ml of methyl iodide was heated on a water bath for 2 h. The methanol was evaporated off, the residue was treated with ether and dissolved in water. The aqueous solution was extracted with ether, treated with charcoal, and evaporated. The amorphous precipitate was ground with ether, then with acetone, and dried in vacuum. The dimethiodide was hygroscopic and did not have a characteristic melting point; it was readily soluble in water and alcohol but difficultly soluble in ether, acetone, and other solvents. Found %: I 29.87; 29.62. $C_{36}H_{52}I_2N_2O_6$. Calculated %: I 29.42.

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