SYNTHESIS OF QUATERNARY AMMONIUM COMPOUNDS CONTAINING NITRODIAMINOPROPANE GROUPS

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The most characteristic feature of compounds with curare-like activity is the presence of two quaternary ammonium groups at a spacing of 14 or 20 Å [1]. During the preparation of accessible myorelaxants with a separation between cationic centers close to optimal we proceeded from the capacity of nitroalcohols to react with amines. 2-Methyl-2-nitro-N, N'-bis-(p-dimethylaminophenyl)-1,3-diaminopropane (III, R = N(CH₃)₂) and tris-(p-dimethylaminophenylaminomethyl)nitromethane (IV, $R = N(CH_3)_2$) were obtained by the reaction of 2-methyl-2-nitro-1,3-propanediol (I) [2] and 2-nitroisobutyl-glycerol (II) [3] with N,N-dimethylp-phenylenediamine and were then converted by the action of methyl iodide into the dimethiodide (III, R =

 $\overset{+}{N}(CH_3)_3$ I⁻) and the trimethiodide (IV, $R = \overset{+}{N}(CH_3)_3$ I⁻), respectively.



According to literature data [1], substitution in the trimethylammonium of even two methyl residues by ethyl causes an increase in curare-like activity. To this end, 2-methyl-2-nitro-N,N'-bis-(p-diethylaminophenyl)-1,3-diaminopropane (III, $R = N(C_2H_5)_2$) was synthesized from (I) and N,N-diethyl-p-phenylenediamine and was converted into the dimethiodide (III, $R = N(C_2H_5)_2CH_3$ I⁻).

The results of pharmacological testing, carried out by A. I. Podlesna in comparison with d-tubocurarine, are presented in Table 1. III, $R = N(CH_3)_3 I^-$ [4] was of the greatest interest having less curare-like activity than d-tubocurarine but being significantly less toxic. It had a greater therapeutic effect and is worthy of mention as a myorelaxant of the pachy-curare type.

EXPERIMENTAL

2-Methyl-2-nitro-N,N'-bis-(p-dimethylaminophenyl)-1,3-diaminopropane (III, $R = N(CH_3)_2$). To a boiling solution of 11 g freshly distilled N,N-dimethyl-p-phenylenediamine and 1 ml triethylamine in 40 ml alcohol was added a solution of 5 g (I) in 35 ml alcohol over 50 min under nitrogen. Heating was continued for 5 h and the solution was then cooled for 48 h at 5°. After crystallization of the precipitate, which had separated from 75 ml alcohol, an orange substance (5 g; 36.5%) of mp 122-124° was obtained.

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TABLE 1. Results of Pharmacological Testing

Compound	Dose causing a curare-like action in mg/kg
III, $R = \overset{+}{N} (CH_3)_3 I^-$	1,0
IV, $R = \overset{+}{N} (CH_3)_3 I^-$	0,3
III, $R = \overset{+}{N} (C_2 H_5)_2 CH_3 I^-$	0,7
d-Tubocurarine	0,1

Found, %: C 64.27, 64.38; H 7.54, 7.68; N 18.65, 18.51. $C_{20}H_{29}N_5O_2$. Calculated, %: C 64.66; H 7.87; N 18.85.

Tris-(p-dimethylaminophenylaminomethyl)nitromethane (IV, R = $N(CH_3)_2$). To a boiling solution of 12.5 g N,N-dimethyl-p-phenylenediamine and 2 ml triethylamine in 50 ml alcohol was added 3.9 g (II) in 50 ml alcohol over 30 min under nitrogen. Heating was continued for 5 h more and the precipitate which had separated on cooling was crystallized from 150 ml acetone. An orange substance (6.1 g; 50%) of mp 156-157° (with decomposition) was obtained. Found, %: C 66.82, 66.61; H 7.85, 7.55; N 19.67, 19.24; mol. wt. 490.1, 503.7. C₂₈H₃₉N₇O₂. Calculated, %: C 66.50; H 7.77; N 19.39; mol. wt. 505.6.

Dimethiodide of 2-Methyl-2-nitro-N,N'-bis-(p-dimethylamino-

phenyl)-1,3-diaminopropane (III, $R = N(CH_3)_3$ I⁻). A mixture of 0.75 g

 $(III, R = N(CH_3)_2)$, 10 ml methanol, and 0.4 ml methyl iodide was heated for 3 h. After crystallization of the solid, which had separated on cooling, from 10 ml water, 0.95 g of a colorless substance of mp 176° (with decomposition) was obtained. Found, %: C 38.46, 38.54; H 6.01, 5.76; I 36.78, 36.80; N 10.07, 9.98. $C_{22}H_{35}I_2N_5O_2 \cdot 2H_2O$. Calculated, %: C 38.22; H 5.38; I 36.70; N 10.13.

Trimethiodide of Tris-(p-dimethylaminophenylaminomethyl)nitromethane (IV, $R = N(CH_3)_3 I^-$). A mixture of 1 g (IV, $R = N(CH_3)_2$), 25 ml methanol, and 0.6 ml methyl iodide was heated for 4 h. The solid which precipitated from the cooled solution was heated with dry acetone, dried in vacuum, and crystallized from 10 ml water with added active charcoal. A yellow substance (0.6 g) of decomposition temperature 190° was obtained. Found, %: I 40.17, 40.26; N 10.01, 10.17. $C_{31}H_{48}I_3N_7O_2 \cdot H_2O$. Calculated, %: I 40.09; N 10.32.

<u>2-Methyl-2-nitro-N,N'-bis-(p-diethylaminophenyl)-1,3-diaminopropane (III, $R = N(C_2H_5)_2$).</u> To a boiling solution of 12.9 g freshly distilled N,N-diethyl-p-phenylenediamine and 2 ml triethylamine in 35 ml alcohol was added a solution of 4.7 g (I) in 40 ml alcohol over 40 min under nitrogen. Heating was continued for 3 h further and the solution then cooled for 48 h. The solution was decanted from the solid which had separated, diluted with water to a slight turbidity, and cooled overnight once again. More solid separated. Both oily solids were dissolved in 100 ml dilute hydrochloric acid, the solution was heated with active charcoal at 50°, and the filtrate poured into concentrated potassium carbonate solution. The oil was extracted with benzene and the extract dried with magnesium sulfate. After distilling off the benzene 9.1 g (66%) of a brown oil was obtained which was not further purified.

 $\begin{array}{l} & \mbox{Dimethiodide of 2-Methyl-2-nitro-N,N'-bis-(p-diethylaminophenyl)-1,3-diaminopropane (III, R = N(C_2H_5)_2CH_3 I^-). A mixture of 5 g (III, R = N(C_2H_5)_2), 10 ml methanol, and 3 ml methyl iodide was heated with stirring for 2 h. The solid, which had separated from the cooled mixture, was crystallized from water containing active charcoal. A slightly greyish substance (3.2 g) of decomposition temperature ~190° was obtained. Found, %: C 43.94, 43.79; H 6.11, 6.24; I 35.76, 35.51; N 9.61, 9.55. C_{26}H_{43}N_5O_2. Calculated, %: C 43.89; H 6.04; I 35.76; N 9.84. \end{array}$

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