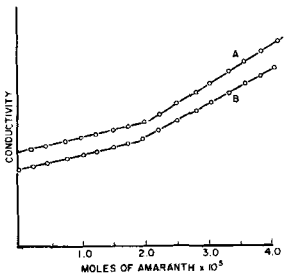

Fig. 3.—Conductimetric titration of CPC and CDBAC with amaranth. Key: A, 5.6 × 10^{-5} moles of CPC; B, 5.06 × 10^{-5} moles of CDBAC.

quaternary ammonium–dye reaction product was formed. Before the end point was reached, the reaction product was kept in solution by the solubilizing effect of the excess quaternary amine and by the charge on the colloidal particles. Both CPC and CDBAC reacted in a ratio of slightly less than 3 moles of quaternary amine to 1 mole of amaranth. The slight departure from the theoretical ratios probably is due to the impurity of the compounds used.

SUMMARY

Data are given to show an interaction between hexylresorcinol or amaranth and two quaternary ammonium germicides. The shape of the titration curves with hexylresorcinol suggest the interaction to be a loose reversible one, probably due to the formation of a mixed micelle (2). In contrast, the interaction of amaranth with the quaternary ammonium compounds is a metathesis reaction of two salts. The conductimetric titration method was found to be a simple and convenient technique for screening compounds for possible interaction with quaternary ammonium compounds.

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Neurodepressive Agents I

By HEINO A. LUTS, W. ZUCARELLO*, and J. F. GRATTAN†

A group of new 3,4,5-trimethoxybenzylamines has been synthesized for pharmacological evaluation. To a degree, all compounds have displayed a depressant effect. Some analgesic, ganglionic blocking, and vasodilating actions have also been exhibited.

IN RECENT YEARS, several papers have been published describing the activity of 3,4,5-trimethoxybenzylamides (1–11) and related compounds. It is noteworthy that these compounds appear to be sedatives for anxiety, agitation, and psychomotor restlessness of the chlorpromazine type instead of the reserpine type, although they contain a structural part (3,4,5-trimethoxybenzyl moiety) of the original reserpine molecule. It has been postulated that chlorpromazine and reserpine act by two distinctly different mechanisms—reserpine by trophotropic stimulation and chlorpromazine by ergotropic inhibition (12). By using molecular models, the structural similarity of the active sites of reserpine and chlorpromazine has been pointed out by Nieforth (13).

In this study, the 3,4,5-trimethoxybenzylamines were prepared by condensing 3,4,5-trimethoxybenzaldehyde with an amine to form an anil, which was not isolated, then reducing it with sodium borohydride to the corresponding secondary amine (Table I).

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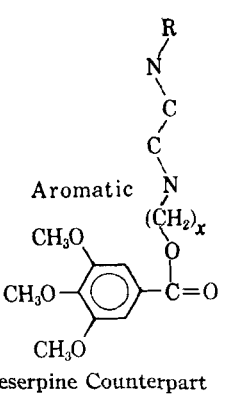
It is suggested that by having a 3,4,5-trimethoxybenzyl base and creating two nitrogen atom sites, then varying the distance between these two, we may be able to create a depressive effect with these two aliphatic nitrogen centers, despite the fact that in chlorpromazine and reserpine one nitrogen is aromatic.

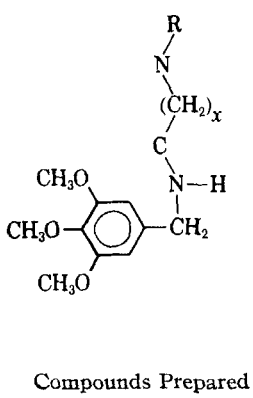
EXPERIMENTAL

General Procedure.—One-tenth mole of 3,4,5-trimethoxybenzaldehyde and 0.1 mole of the desired amine were mixed with 100 ml. of xylene and refluxed for 20 hours with a water separator attached to the condenser. After the theoretical amount of water was separated, the xylene was distilled off under reduced pressure. The compound was then taken

Schematic Sketch of the Molecules

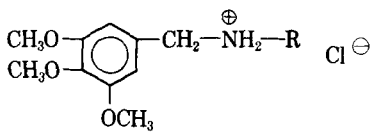


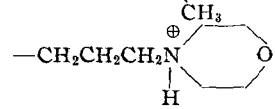
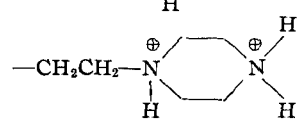
Reserpine Counterpart



Compounds Prepared

TABLE I.—3,4,5-TRIMETHOXYBENZYLAMINO DERIVATIVES



No.	R		Over-All Yield	Mol. Wt.	M.p., °C.	Formula	Anal., N Calcd.	Found
1	$-CH_2CH_2CH_2\overset{\oplus}{N}(CH_2CH_3)_2-H$	$Cl^\ominus$	87	383.34	175	$C_{17}H_{32}Cl_2N_2O_3$	7.04	6.75
2	$-CH_2CH_2CH_2\overset{\oplus}{N}(CH_3)(CH_3)-H$	$Cl^\ominus$	89	354.92	208–210	$C_{15}H_{28}Cl_2N_2O_3$	7.88	8.20
3		$Cl^\ominus$	67	397.33	153–155	$C_{17}H_{30}Cl_2N_2O_4$	7.05	7.20
4		$2Cl^\ominus$	56	418.79	105–106	$C_{16}H_{30}Cl_3N_3O_3$	10.03	9.82
5	$-CH_2CH(OH)-CH_3$		74	291.78	165–166	$C_{13}H_{22}ClNO_4$	4.80	4.75
6	$-CH_2CH_2\overset{\oplus}{N}H(CH_2CH_2OH)-H$	$Cl^\ominus$	72	357.26	243–245	$C_{14}H_{26}Cl_2N_2O_4$	7.84	7.71
7	$-CH_2CH_2\overset{\oplus}{N}(CH_2CH_3)(CH_2CH_3)-H$	$Cl^\ominus$	82	368.32	184–187	$C_{16}H_{30}Cl_2N_2O_3$	7.40	7.30

up in 50 ml. of methanol and reduced with 5.6 Gm. (0.15 mole) of sodium borohydride. After refluxing for 30 minutes, the methanol was removed by distillation, 50 ml. of water added, and the residue cooled. The remaining mixture was then extracted twice with 50-ml. portions of ether. The extracts were then combined, dried over anhydrous calcium sulfate,[1] and acidified with anhydrous hydrogen chloride. The crystals were collected and washed with dry ether.

SUMMARY

Pharmacology.—The preliminary pharmacological findings demonstrate that compound *1* is a mild stimulant having no effect on hexobarbital[2] and muscle paralysis; it also exhibited vasodilating effect. Compound *2* is a depressant with no hypothermic effect and slight analgesic properties. Compound *3* had variable hypothermic effect and also exhibited ganglionic blocking properties. Compound *4* also showed depressant properties, definite hypothermic effect, and was a ganglionic blocker. In addition to this, it also showed definite analgesic properties, but no anti-inflammatory properties were observed. Compound *5* exhibited depressant properties and slight hypothermia in rats. Compound *6* is a somewhat milder depressant and also shows slight antispasmodic effect. The depressant activity of compound *7* is somewhat poorer than the others.

[1] Marketed as Drierite by W. A. Hammond Drierite Co., Xenia, Ohio.

[2] Marketed as Evipal by Winthrop Laboratories, New York, N. Y.

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