(2.4 g.) and triethylamine (3.6 g.). The free base was a yellow oil, yield 4.3 g. (93%).

**Acknowledgments.**—The authors wish to thank Mr. A. Amato for technical assistance; Dr. M. Marzadro and her associate for the microanalyses.

---

# The Effect of Methoxyphenyl Substitutions on the Strychnine-Like Activity of Aryldiazaadamantanones and Aryldiazaadamantanols[1]

S. CHIAVARELLI, L. V. FENNOY,[2] G. SETTIMJ, and LEONOR DE BARAN[3]

*Laboratorio di Chimica Terapeutica, Istituto Superiore di Sanita, Rome, Italy*

*Received July 18, 1962*

The synthesis and pharmacological testing of eight new phenyl substituted diazaadamantanols and six new phenyl substituted diazaadamantanones are reported. In most cases, the effect of methoxyl substitution in the aromatic rings of phenyldiazaadamantanones was to change the activity from a strychnine-like to a non-convulsive one. The diazaadamantanol's strychnine-like activity was lowered by these phenyl substitutions. In two cases, the 3,4-dimethoxy and the 3,4,5-trimethoxy derivatives, the convulsive activity disappeared completely.

Chiavarelli, Settimj, and Magalhaves Alves[4] synthesized a compound following the method of Kyi and Wilson,[5] which was believed to be 1,5-diphenyl-3,7-bispidin-9-one. Reduction of this bispidinone with lithium aluminum hydride gave what was also believed to be the corresponding 1,5-diphenyl-3,7-bispidin-9-ol. Preliminary screening of this compound showed that it had strychnine-like activity. Further chemical studies[6] proved the first compound to be 1,5-diphenyl-3,7-diazaadamantan-9-one and the second to be 1,5-diphenyl-3,7-diazaadamantan-9-ol.

(1) This investigation was carried out during the tenure of a Post-doctoral Fellowship (L.V.F.) from the National Institute of Neurological Diseases and Blindness, United States Public Health Service.

(2) To whom correspondence should be sent: Department of Chemistry, St. Louis University, St. Louis, Missouri.

(3) Fellow of Consejo Nacional de Investigaciones scientificas y technicas, Argentina.

(4) S. Chiavarelli, G. Settinj, and H. Magalhaves Alves, *Gazz. chim. ital.*, **89**, 110 (1957).

(5) Zu-Yoong Kyi and W. Wilson, *J. Chem. Soc.*, 1706 (1951).

(6) S. Chiavarelli and G. Settimj, *Gazz. chim. ital.* **88**, 1234 (1958).

The strychnine-like properties of 1,5-diphenyl-3,7-diazaadamantan-9-ol were further studied by Longo, Silvestrini and Bovet.[7] This was the first reported case of a synthetic compound having true strychnine activity. On a weight basis 1,5-diphenyl-3,7-diazaadamantan-9-ol is about one third as active as strychnine in the mouse and rabbit and about one half as active in the rat.

The activity of 1,5-diphenyl-3,7-diazaadamantan-9-ol created interest in other compounds with similar structures. Alkylation[8] of the 9-position of this diazaadamantanol with various alkyl groups decreased its strychnine-like activity. The precursor to 1,5-diphenyl-3,7-diazaadamantan-9-ol, 1,5-diphenyl-3,7-diazaadamantan-9-one was about $^1/_{30}$th as active in the rabbit and $^1/_{60}$th as active in the mouse as the diazaadamantanol.

In this paper are reported the synthesis and the pharmacological testing of eight new phenyl substituted diazaadamantanols (Table I) and six new phenyl substituted diazaadamantanones (Table II). Three of the reported diazaadamantanones; the *o*-methoxy, the *p*-methoxy and the 3,4-dimethoxy derivatives were previously reported[4] to be bispidinones. All of the diazaadamantanones were prepared by the Mannich reaction[6] using the appropriate ketone. The diazaadamantanols were obtained by reducing the corresponding diazaadamantanones with lithium aluminum hydride,[6] with the exception of the two 9-alkyl diazaadamantanols which were prepared by the method of Chiavarelli and Fennoy.[8]

## Experimental[9,10]

The following methods of preparation were typical of the synthetic method used for each class of compounds.

**1,3-Bis(3,4,5-trimethoxyphenyl)acetone.**—Lead 3,4,5-trimethoxyphenylacetate[4] (25 g., 0.038 mole) was pyrolyzed in a 500 ml. cracking flask under reduced pressure. The pressure at the beginning of the decomposition was 0.02 mm. and rose to 3 mm. at which point a yellow compound distilled between 190° to 235°. The yield was 7 g. (48%). After one recrystallization from absolute alcohol, the pure compound melted at 99–101°.

*Anal.* Calcd. for $C_{21}H_{26}O$: C, 64.58; H, 6.71. Found: C, 64.58; H, 6.49.

**1,5-Di(3,4,5-trimethoxyphenyl)-3,7-diazaadamantan-9-one.**—A mixture of 1,3-bis(3,4,5-trimethoxyphenyl)acetone (1.9 g., 0.005 mole), paraformaldehyde (0.94 g., 0.025 mole) and ammonium acetate (0.77 g., 0.01 mole) in 5 ml. of absolute ethanol was refluxed on a water bath for 5 hr. The mixture was cooled in the re-

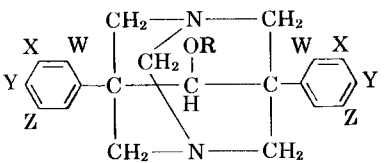
(7) V. G. Longo, B. Silvestrini, and D. Bovet, *Boll. Soc. it. Biol. Sper.*, **34**, 1866 (1958). Also see *J. Pharmacol. Exptl. Therap.*, **126**, 41 (1959).

(8) S. Chiavarelli and L. V. Fennoy, *J. Org. Chem.*, **26**, 4895 (1961).

(9) All melting points were taken in a capillary tube and are uncorrected.

(10) The recrystallizing solvent was ethanol for all the diazaadamantanones and all the diazaadamantanols except the 3,4,5-trimethoxydiazaadamantanol.

TABLE I

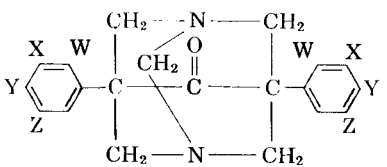


PHENYL SUBSTITUTED DIAZAADAMANTANOLS

| W | X | Y | Z | R | M.p., °C. | Yield, % | Formula | Analyses, % Calcd. C | H | N | Found C | H | N | Toxicity[a,b] mg./kg. Mouse | Rabbit |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| H | H | H | H | H | 278–279 | 87 | $C_{20}H_{22}N_2O$ | 78.40 | 7.24 | 9.14 | 78.38 | 7.44 | 9.00 | 1.5 S | 1.2 |
| H | $CH_3$ | H | H | H | 207–208 | 75 | $C_{22}H_{26}N_2O$ | 79.00 | 7.84 | 8.38 | 78.81 | 7.73 | 8.47 | 7.5 S | 1.5 |
| $OCH_3$ | H | H | H | H | 225–226 | 60 | $C_{22}H_{26}N_2O_3$ | 72.10 | 7.15 | 7.65 | 72.28 | 7.13 | 7.42 | 20 S | 7 |
| H | $OCH_3$ | H | H | H | 197–198 | 60 | $C_{22}H_{26}N_2O_3$ | 72.10 | 7.15 | 7.65 | 71.89 | 7.54 | 7.62 | 10 S | 4 |
| H | H | $OCH_3$ | H | H | 239–240 | 60 | $C_{22}H_{26}N_2O_3$ | $OCH_3$, 17.52 | 7.65 | | $OCH_3$, 17.35 | 7.85 | | 3.5 S | 5 |
| H | $OCH_3$ | $OCH_3$ | H | H | 191–193 | 25 | $C_{24}H_{30}N_2O_5$ | $OCH_3$, 29.74 | 6.57 | | $OCH_3$, 29.44 | 6.76 | | 300 NC | |
| H | $OCH_3$ | $OCH_3$ | $OCH_3$ | H | 207–208 | 70 | $C_{26}H_{34}N_2O_7$ | 64.18 | 7.04 | 5.76 | 64.26 | 7.30 | 5.66 | X | |
| H | H | $OCH_3$ | H | $CH_3$ | 233–234 | 95 | $C_{23}H_{28}N_2O_3$ | 72.60 | 7.42 | 7.35 | 72.44 | 7.47 | 7.16 | 100 C | |
| H | H | $OCH_3$ | H | $CH_3CH_2$ | 264 | 95 | $C_{24}H_{30}N_2O_3$ | 73.07 | 7.66 | 7.10 | 72.76 | 7.82 | 7.07 | 150 C | |
| | Strychnine | | | | | | | | | | | | | 0.4 S | 0.04 |

[a] The intraperitoneal $LD_{50}$ in mice was calculated using the probit method; for rabbits intravenous administration. The LD figures are approximate. [b] S = strychnine-like, C = convulsive, NC = non convulsive, X = no activity.

TABLE II



PHENYL SUBSTITUTED DIAZAADAMANTANONES

| W | X | Y | Z | M.p., °C. | Yield, % | Formula | Analyses, % Calcd. C | Calcd. H | Calcd. N | Found C | Found H | Found N | Toxicity[a,b] Mouse | mg./kg. Rabbit |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| H | H | H | H | 263–264 | 59 | $C_{20}H_{20}N_2O$ | 78.92 | 6.62 | 9.20 | 78.81 | 7.77 | 9.03 | 67 SS | 440 |
| H | $CH_3$ | H | H | 172–173 | 60 | $C_{22}H_{24}N_2O$ | 79.48 | 7.28 | 8.43 | 79.69 | 7.29 | 8.51 | 500 S | |
| $OCH_3$ | H | H | H | 240–242 | 22 | $C_{22}H_{24}N_2O_3$ | 72.50 | 6.64 | 7.69 | 72.60 | 6.75 | 7.80 | 20 S | 66 |
| H | $OCH_3$ | H | H | 201–203 | 50 | $C_{22}H_{24}N_2O_3$ | 72.50 | 6.64 | 7.69 | 72.56 | 6.71 | 7.86 | 300 NC | |
| H | H | $OCH_3$ | H | 215–216 | 60 | $C_{22}H_{24}N_2O_3$ | $OCH_3$, 17.62 | 7.69 | | $OCH_3$, 17.68 | 7.69 | | 35 NC | 10 |
| H | $OCH_3$ | $OCH_3$ | H | 153–155 | 45 | $C_{24}H_{28}N_2O_5$ | 67.93 | 6.65 | 6.60 | 67.82 | 6.90 | 6.72 | 100 NC | 20 |
| H | $OCH_3$ | $OCH_3$ | $OCH_3$ | 231–232 | 33 | $C_{26}H_{32}N_2O_7$ | 64.45 | 6.66 | 5.78 | 64.34 | 6.80 | 6.80 | X | |
| | Strychnine | | | | | | | | | | | | 0.4 S | 0.4 |

[a] The intraperitoneal $LD_{50}$ in mice was calculated using the probit method; for rabbits intravenous administration. The LD figures are approximate. [b] Strychnine-like, C = convulsive, NC = non-convulsive, X = no activity.

frigerator overnight and the crystalline product was removed by filtration. The yield was 0.8 g. (33%). After one recrystallization from ethanol the melting point was 231–232°.

**1,5-Di(3,4,5-trimethoxyphenyl)-3,7-diazaadamantan-9-ol.**—A solution of the above diazaadamantanone (0.97 g., 0.002 mole) in 90 ml. of tetrahydrofuran was added all at once to a clear solution of lithium aluminum hydride (0.1 g.) in 90 ml. of tetrahydrofuran and the resulting solution refluxed for 8 hr. The reaction mixture was cooled and decomposed with the minimum amount of water and filtered hot. Upon concentration of the filtrate, there was obtained a white solid 0.68 g. (70%), m.p. 192–95°. Recrystallization from methanol raised the melting point to 206–207°.

**Pharmacology.**—The compounds prepared during the present work were tested for strychnine-like activity. All were crystalline bases. The test solutions were prepared by dissolving the bases in the calculated volume of *N* hydrochloric acid and diluting with distilled water. The toxicity studies were carried out with white mice and rabbits. Only the compounds that had a $LD_{50}$ (in mice) less than 100 mg./kg. were tested in the rabbit. The mice were injected intraperitoneally and the rabbits intravenously.

As was previously noted, both 1,5-diphenyl-3,7-diazaadamantanone and 1,5-diphenyl-3,7-diazaadamantanol had strychnine-like activity. The reported substitutions on the phenyl groups of 1,5-diphenyl-3,7-diazaadamantanone caused the strychnine-like activity to disappear completely, except in the case of the *o*-methoxy derivative which demonstrated an activity which increased markedly over that of its precursor 1,5-diphenyl-3,7-diazaadamantanone. In the case of the substitutions on the phenyl groups of 1,5-diphenyl-3,7-diazaadamantanol, the strychnine-like activity was lowered somewhat but retained; however, there were two exceptions, the 3,4-dimethoxy and the 3,4,5-trimethoxy derivatives in which it disappeared completely. Chiavarelli and Fennoy[8] have shown that alkylation of the 9-position of diazaadamantanol merely reduces its strychnine-like activity. The 9-methyl or 9-ethyldiazaadamantanols were found to be only convulsive when methoxy groups were substituted in the *para* positions.

**Acknowledgment.**—We are indebted to Dr. M. Marzadro for the microanalyses.