The compounds tested in these trials were incorporated into a standard ration and fed to the birds for 2 days prior to infection and continued for the duration of the test.

The anticoccidial efficacy in these experiments was based on three factors: (1) mortality, (2) weight gain or loss, and (3) droppings scores. The primary criterion of efficacy was the mortality produced in the medicated-infected chicks as compared to the nonmedicated-infected chicks. Droppings scores and ratios of mean weight gains, medicated-infected *vs.* nonmedicated-noninfected, were used as indicators of morbidity.[6]

Acknowledgment.—The authors wish to acknowledge Mrs. Carol Barker and Mr. Marvin Carr for obtaining the analytical data and assisting with the experiments.

(6) R. R. Baron, M. W. Moeller, and N. F. Morehouse, *Poultry Sci.*, **45**, 411 (1966).

New Compounds

Synthesis of 3,5-Dihydroxy-4-methoxy-α-methylphenethanolamine and Analogs

FRED G. H. LEE, DONALD E. DICKSON, JOSEPH D. BENIGNI, R. L. MINNIS, WALTER F. GANNON

Regis Chemical Company, Chicago, Illinois 60610

AND ALBERT A. MANIAN

Psychopharmacology Research Branch, National Institute of Mental Health, Chevy Chase, Maryland 20203

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Numerous endogenous amines were synthesized by this laboratory during the past several years.[1] 3,5-Dihydroxy-4-methoxy-α-methylphenethylamine and its phenethanolamine analog were found recently to be among the most active releasing agents for cardiac norepinephine-3H.[2] Such results have prompted us to report our syntheses.

Experimental Section[3]

3,5-Dibenzyloxy-4-methoxy-β-methyl-β-nitrostyrene.—A mixture of 2.40 g of NH_4OAc, 0.73 ml of Ac_2O, and 2.40 ml of AcOH was heated to 60° for 15 min. To the mixture was added 1.40 g (4.0 mmoles) of 3,5-dibenzyloxy-4-methoxybenzaldehyde, 15 ml of AcOH, and 40 ml of $EtNO_2$. The mixture was stirred and heated to reflux, using a Dean-Stark water separator. After the addition of 1.75 g of NaOAc and 6 ml of AcOH, the distilled $EtNO_2$ was replaced three times in the 2-hr reflux period. The separator was removed and excess $EtNO_2$ was removed under vacuum. The mixture was cooled and washed with H_2O. A semisolid resulted which was crystallized from MeOH to give 4.30 g (45.8%), mp 97–99°. *Anal.* ($C_{24}H_{23}NO_5$) C, H, N.

Similarly, other substituted β-nitrostyrenes have been prepared and the results are summarized in Table I.

1-(3,5-Dibenzyloxy-4-methoxyphenyl)-2-methyl-2-nitroethanol.—To a solution of 10.5 g (30 mmoles) of 3,5-dibenzyloxy-4-methoxybenzaldehyde in 354 ml of EtOH at 5° was added 6.7 g (89 mmoles) of $EtNO_2$. The temperature was maintained at 5° and with stirring a solution of 1.75 g (31 mmoles) of NaOH in 6.5 ml of H_2O was added dropwise over 10 min. The mixture was stirred at 5° for 1 hr and then poured into 820 ml of 2% AcOH at 0° very slowly. The product was extracted [$(ClCH_2)_2$], dried (Na_2SO_4), concentrated to dryness, and crystallized from C_6H_6–C_6H_{14} to yield in two crops 3.25 g (25.7%) of product, mp 110–113°. *Anal.* ($C_{24}H_{23}NO_6$) C, H, N.

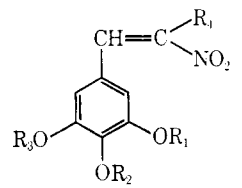
Other β-nitrophenethanols are listed in Table II.

3,5-Dihydroxy-4-methoxy-α-methylphenethanolamine Hydrochloride.—To a Parr shaker were charged 3.25 g (7.7 mmoles) of 1-(3,5-dibenzyloxy-4-methoxyphenyl)-2-methyl-2-nitroethanol dissolved in 140 ml of EtOH, 0.75 g of PtO_2, and 2.1 kg/cm² of H_2. The mixture was shaken for 25 min, the catalyst was filtered and replaced with 1.10 g of 10% Pd-C, and the mixture again was shaken under 2.1 kg/cm² for 27 min. The catalyst was filtered and washed with EtOH and the combined filtrates were made acidic with alcoholic HCl and taken to dryness. The residue was crystallized from EtOH–Et_2O to yield in three crops 0.160 g (8.34%) of product, mp 252–254° dec. *Anal.* ($C_{10}H_{15}NO_4 \cdot HCl$) C, H, N.

Similarly, other substituted phenethanolamines have been prepared and the results are summarized in Table III.

3,5-Dihydroxy-4-methoxy-β-methylphenethylamine Hydrochloride.—To a solution of 4.0 g (100 mmoles) of LAH dissolved

TABLE I
SUBSTITUTED β-NITROSTYRENES



R_1	R_2	R_3	R_4	Mp, C°	Yield, %	Formula	Analyses
CH_3	$C_6H_5CH_2$	CH_3	H	133	79	$C_{17}H_{17}NO_5$	C, H, N[a]
CH_3	CH_3	$C_6H_5CH_2$	H	103–105	49.4	$C_{17}H_{17}NO_5$	C, H, N[b]
CH_3	CH_3	CH_3	H	115–119	67	$C_{11}H_{13}NO_5$	C, H, N[c]
$C_6H_5CH_2$	CH_3	$C_6H_5CH_2$	CH_3	97–99	45.8	$C_{24}H_{23}NO_5$	C, H, N

[a] K. Ratzl, T. Horejachi, and G. Gillek, *Monatsh.*, **85**, 1154 (1954). [b] E. Späth and H. Röder, *ibid.*, **43**, 93 (1922). [c] E. Späth, *ibid.*, **40**, 129 (1919).

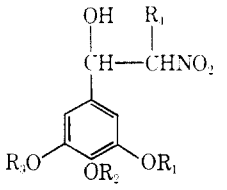
(1) This investigation was supported by the Psychopharmacology Research Branch, National Institute of Mental Health, Contract SA-43-ph-3021.

(2) C. R. Creveling, J. W. Daly, and B. Witkop, *J. Med. Chem.*, **11**, 595 (1968).

(3) Melting points are corrected. Where analyses are indicated by symbols of the elements, analytical results obtained were within ±0.4% of the theoretical values. Spectral data were in agreement with assigned structures.

TABLE II

SUBSTITUTED β-NITROPHENETHANOLS

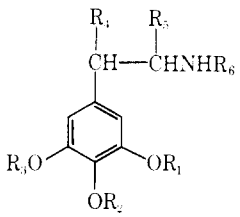


R_1	R_2	R_3	R_4	Mp, °C	Yield, %	Formula	Analyses
$C_6H_5CH_2$	CH_3	$C_6H_5CH_2$	H	131–133	66.0	$C_{23}H_{23}NO_6$	C, H, N
CH_3	CH_3	$C_6H_5CH_2$	H	119–121	94.4	$C_{17}H_{19}NO_6$	C, H, N
CH_3	$C_6H_5CH_2$	CH_3	H	112–114	40.0	$C_{17}H_{19}NO_6$	C, H, N[a]
$C_6H_5CH_2$	CH_3	$C_6H_5CH_2$	CH_3	111–113	25.7	$C_{24}H_{25}NO_5$	C, H, N

[a] R. A. Heacock, O. Hutzinger, and C. Nerenberg, *Can. J. Chem.*, **39**, 1143 (1961).

TABLE III

SUBSTITUTED PHENETHYLAMINES AND PHENETHANOLAMINES



R_1	R_2	R_3	R_4	R_5	R_6	Mp, °C	Yield, %	Formula[a]
CH_3	H	CH_3	H	H	H	256–258	87	$C_{10}H_{15}NO_3 \cdot HCl$
CH_3	CH_3	H	H	H	CH_3	159–161	35.6	$C_{11}H_{17}NO_3 \cdot HCl$
CH_3	H	CH_3	H	H	CH_3	173–174	45.4	$C_{11}H_{17}NO_3 \cdot HCl$
CH_3	CH_3	CH_3	H	H	CH_3	190–192	31.0	$C_{12}H_{19}NO_3 \cdot HCl$
CH_3	CH_3	CH_3	H	H	COOEt	66–68	71.2	$C_{14}H_{21}NO_5$
H	CH_3	H	H	CH_3	H	228–230	77	$C_{10}H_{15}NO_3 \cdot HCl$
H	CH_3	H	OH	H	H	202–203	56	$C_9H_{13}NO_4$
CH_3	CH_3	H	OH	H	H	154–156	43	$C_{10}H_{15}NO_4$
CH_3	H	CH_3	OH	H	H	191–193 dec	98.1	$C_{10}H_{15}NO_4$
H	CH_3	H	OH	CH_3	H	254–255 dec	8.72	$C_{10}H_{15}NO_4 \cdot HCl$

[a] All compounds were analyzed for C, H, N.

in 150 ml of dry THF was added dropwise over 30 min a solution of 4.2 g (18.4 mmoles) of 3,5-dibenzyloxy-4-methoxy-β-methyl-β-nitrostyrene in 40 ml of THF. The suspension was heated to reflux and stirred for 6 hr, then decomposed with 30 ml of H_2O in 120 ml of THF. After heating to reflux for 0.5 hr the salts were filtered and washed several times with hot THF and the combined filtrates were taken to dryness. The residue was dissolved in a little EtOH and made acidic with alcoholic HCl, and the resulting product was crystallized from EtOH–Et_2O to yield 2.35 g (54.5%) of product, mp 129–131° dec. The compound was not further characterized and was used directly in the next step.

To a Parr shaker were charged 2.10 g (5 mmoles) of 3,5-dibenzyloxy-4-methoxy-β-methylphenethylamine hydrochloride in 150 ml of EtOH, 0.30 g of 10% Pd–C, and 2.1 kg/cm² of H_2. The contents were shaken for 48 min, during which time the theoretical amount of H_2 was taken up. The catalyst was filtered, and the filtrate was taken to dryness and crystallized from EtOH–Et_2O to yield 0.90 g (77.0%) of product, mp 228–230° dec. *Anal.* ($C_{10}H_{15}NO_2 \cdot HCl$) C, H, N.

Similarly, other substituted phenethylamines have been prepared and the results are summarized in Table III.

N-Methylation of Phenethylamines. A. Formylation Method.—To 14 ml of formic–acetic anhydride, cooled in an ice bath, was added slowly 0.04 mole of the phenethylamine. The resulting solution was allowed to stand at room temperature for 5 hr. Ether (110 ml) was added and the solution was allowed to stand for 16 hr. The Et_2O solution was washed successively with H_2O, dilute NH_4OH, brine, and H_2O. The dried Et_2O solution was taken to dryness, and the residue was reduced with diborane[4] to yield the corresponding N-methylphenethylamines.

B. Carbamate Method.—To an ice-cold solution of 2.10 g (0.01 mole) of mescaline[5] in 50 ml of H_2O, 0.60 g (0.006 mole) of ethyl chloroformate was added dropwise with vigorous stirring and external cooling to maintain the temperature at 5–10°. A solution of 0.50 g (0.012 mole) of NaOH in 5 ml of H_2O then was added dropwise simultaneously with a second 0.60-g (0.012 mole) portion of ethyl chloroformate, and the mixture was stirred for an additional 1 hr at 5–10°. The solid was filtered, washed well with H_2O, and dried to yield 2.0 g (71.2%) of ethyl N-[β-(3,4,5-trimethoxyphenyl)]ethylcarbamate, mp 37–40°. After two recrystallizations from C_6H_6–C_6H_{14}, light brown crystals were obtained, mp 66–68°. *Anal.* ($C_{14}H_{21}NO_5$) C, H, N.

N-Methyl-3,4,5-trimethoxyphenethylamine was obtained by LAH reduction of the corresponding ethyl carbamate.

(4) H. C. Brown and P. Heim, *J. Am. Chem. Soc.*, **86**, 3566 (1964).

(5) See footnote c in Table I.