

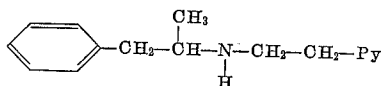
1

3,055,906 PYRIDYLETHYLATED *d*- α -METHYL- PHENETHYLAMINES

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This invention is concerned with pyridylethylated *d*- α -methylphenethylamines and derivatives thereof which are effective agents in modifying central nervous system activity. In particular, the invention is concerned with pyridylethylated *d*- α -methylphenethylamines of the structure shown



2

vinylpyridine being derived from the group consisting of 2- and 4-vinylpyridine and the ring alkylated derivatives of 2- and 4-vinylpyridines. The most efficient procedure has proven to be the acetic acid catalyzed condensation as described by Reich and Levine, J. Am. Chem. Soc., 77: 5434 (1955).

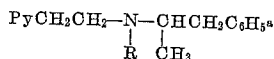
After a suitable reaction period under reflux, the products are collected by fractional distillation. The amines are secondary amines and can be readily converted to their mono- and dihydrochlorides and similar acid salts.

In turn, the secondary amine is readily acylated or aroylated upon treatment with acid chlorides of the type RCOCl wherein R has the significance described above.

The acylated and aroylated derivatives upon treatment with mineral acids give the corresponding acid salts and upon treatment with lower alkyl halides or sulfates afford the corresponding quaternary ammonium salts.

Typical compounds representing the structural ambit of this invention are described in the table below:

TABLE

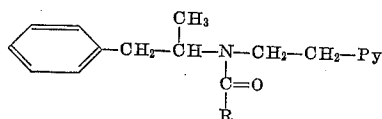


No.	R	M.P. ^{b, c} or B.P. ^c , °C. (Mm.)	Yield, ^d per- cent	Formula	Analyses ^e					
					Carbon, per- cent		Hydrogen, per- cent		Nitrogen, per- cent	
					Calcd.	Found	Calcd.	Found	Calcd.	Found
1	H	120 (0.05)	≈ 66	C ₁₆ H ₂₀ N ₂	80.0	80.1	8.4	8.2	11.7	12.0
2	CH ₃ CO—	170–179 (0.16)	87	C ₁₈ H ₂₂ N ₂ O					9.9	10.1
3	(f)	151–152 ^{ca}	85	C ₁₉ H ₂₂ IN ₂ O	53.8	54.0	5.9	6.0	6.6	6.8
4	p-CH ₃ OC ₆ H ₄ CO—	235–242 (0.03)	39	C ₂₄ H ₂₈ N ₂ O ₂	77.0	77.0	7.0	6.7	7.5	7.0
5	o-C ₂ H ₅ OC ₆ H ₄ CO—	226–229 (0.03)	47	C ₂₅ H ₂₈ N ₂ O ₂					7.2	6.8
6	TMB ^b	117–118 ^{cb}	58	C ₂₆ H ₃₀ N ₂ O ₄	71.9	71.7	7.0	7.2	6.5	6.0
7 ^{aa}	H	128–134 (0.08)	≈ 53	C ₁₆ H ₂₀ N ₂	80.0	79.5	8.4	8.4	11.7	11.7
8 ^{aa}	o-C ₂ H ₅ OC ₆ H ₄ CO—	103–106 ^{cb}	57	C ₂₅ H ₂₈ N ₂ O ₂	77.3	77.4	7.3	7.1	7.2	6.9
9 ^{ab}	H	148–150 (0.4)	≈ 46	C ₁₈ H ₂₄ N ₂	80.6	80.7	9.0	9.1	10.4	9.8

^a Py=2-pyridyl unless otherwise indicated; ^{aa} Py=4-pyridyl; ^{ab} Py=5-ethyl-2-pyridyl.
^b Melting points are not corrected and were established on a Fisher-Johns melting point block.
^c Recrystallizing solvent; ^{ca} ethyl acetate; ^{cb} hexane-benzene.
^d Yields are expressed as recrystallized or distilled product.
^e Analyses are by Weiler and Strauss, Oxford, England.
^f Compound is methiodide of compound 2.
^g [α]_D²⁰ in methanol; compound 1, +21.40; compound 7, +24.30; compound 9, +22.30.
^h TMB=3,4,5-trimethoxybenzoyl.

wherein Py is selected from the group of 2- and 4-pyridyl and alkylated 2- and 4-pyridyl.

In addition, the invention comprises acylated aroylated derivatives of the compounds of the formula above which can be represented by the structure below:



wherein R is lower alkyl, phenyl and substituted phenyl and said substituted phenyl is selected from the group consisting of lower alkoxyphenyl and 3,4,5-trimethoxy.

The compounds of this invention on testing show diverse yet unambiguous response in their effect on the central nervous system in that they either promote central nervous system activity or significantly depress such activity.

While the exact mechanism of the pharmacological response to the compounds of this invention is as yet unknown, it would appear that they act and mediate central nervous system responses which, depending on the structure of the compound involved, are observable as a depressant or analeptic pharmacological response.

The pyridylethylated *d*- α -methylphenethylamines of this invention are conveniently prepared by condensation of *d*- α -methylphenethylamine with a vinylpyridine, said

The invention will be further illustrated by description in connection with the following specific examples showing the preparation of compounds of the invention.

Example 1

N-*d*- α -methylphenethyl-2-(5-ethyl-2-pyridyl)ethylamine (Compound 9).—A mixture of one-third mole each of *d*- α -methylphenethylamine, 2-vinyl-5-ethylpyridine, and acetic acid in 80 ml. of methanol was heated under reflux for 8 hours and distilled. After removal of low boiling fractions, a forerun was collected at 128–140° (0.3 mm.), and the product (41.5 g.) was obtained, B.P. 148–150° (0.4 mm.). The forerun, upon trituration with hexane, gave 2.4 g. (4.1%), M.P. 126–127°, not depressing the melting point of authentic *d*- α -methylphenethylacetamide.

Compounds 1 and 7 were similarly prepared.

Example II

Acetamide of Compound 1 (Compound 2).—A mixture of 9.6 g. (0.04 mole) of Compound 1 and 10 ml. of acetic anhydride was heated under reflux for 1 hour. When cool, after addition of 100 ml. of water, and basification, the formed oil was extracted with 100 ml. of benzene and the product was obtained by distillation, 9.77 g. (87%), B.P. 170–179° (0.16 mm.).

3

A solution of 2.8 g. (0.01 mole) of the compound in 25 ml. of acetonitrile and 2 ml. of methyl iodide was refluxed for 2 hours, and upon cooling, yielded 3.6 g. (85%) of the methiodide (Compound 3). Attempted hydrogenation with rhodium on carbon afforded only un-

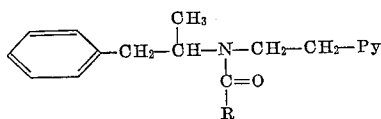
Example III

3,4,5-trimethoxybenzamide of Compound 1 (Compound 6).—A solution of 9.6 g. (0.04 mole) of compound 1 in 35 ml. of benzene was added dropwise under stirring over 1 hour to a solution of 4.6 g. (0.02 mole) of 3,4,5-trimethoxybenzoyl chloride in 65 ml. of benzene while maintaining the temperature at 25–30°. When addition was complete, the reaction mixture was heated under reflux for 1 hour and then stored at 20° for 24 hours. After extraction with dilute hydrochloric acid, and basification, 8.6 g. (98%) of product was separated and recrystallized.

It is to be noted that it is intended to cover all changes and modifications of the examples of the invention herein chosen for the purpose of illustration which do not constitute departures from the spirit and scope of the invention.

We claim:

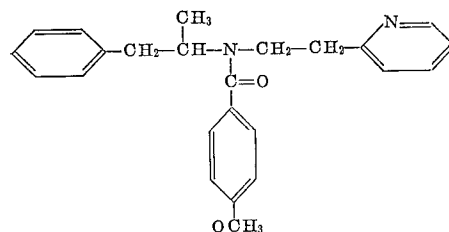
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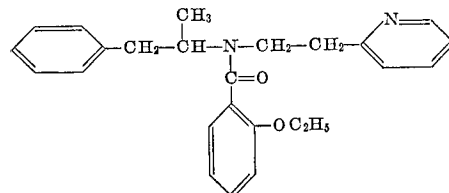
wherein Py is selected from the group consisting of 2-pyridyl, 4-pyridyl, and 2-pyridyl-5-ethyl and R is selected from the group consisting of lower alkyl, phenyl, lower alkoxyphenyl, and 3,4,5-trimethoxyphenyl.

2. The compound of the formula

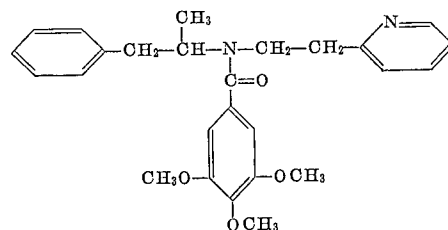
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3. The compound of the formula



4. The compound of the formula



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