ture of 1.00 g (1.92 mmoles) of **2d**, 200 ml of dry Et_2O, and 0.539 g (4.80 mmoles) of KO-*t*-Bu (K & K Laboratories) was stirred at room temperature for 30 min (progress of reaction followed by ir spectroscopy). The reaction mixture was filtered with suction and the filtrate was evaporated under reduced pressure at 35°. The solid residue was recrystallized from heptane to afford 0.441 g (64%) of **1a**: mp 100.5–102.0°; ir, 1832 cm^{-1}; nmr τ 7.47 (2 H, s), 7.67–8.60 (14 H, m), 8.75 (18 H, s). *Anal.* ($C_{22}H_{34}N_2O_2$) C, H, N.

1,3-Bis[1-(1-adamantyl)-2-oxo-3-aziridinyl]adamantane (1b).—A mixture of 1.00 g (1.48 mmoles) of **2e**, 200 ml of dry Et_2O, and 0.414 g (3.70 mmoles) of KO-*t*-Bu (K & K Laboratories) was stirred at room temperature for 30 min, and worked up as described above to furnish, after recrystallization from heptane, 0.456 g (60%) of **1b**: mp ~180–190° dec; ir, 1832 cm^{-1}; nmr τ 7.40 (2 H, s), 7.41–8.79 (44 H, m). *Anal.* ($C_{34}H_{46}N_2O_2$) C, H, N.

Derivatives of 2,5-Dimethoxy-4-methylamphetamine (DOM)[1]

Beng T. Ho, L. Wayne Tansey, and William M. McIsaac

Texas Research Institute of Mental Sciences, Houston, Texas 77025

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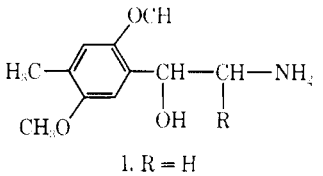
During the course of our investigation on psychotomimetic compounds,[2,3] 2,5-dimethoxy-4-methylphenethanolamine (I) and 2,5-dimethoxy-4,α-dimethylphenethanolamine (II) were synthesized. These two compounds might possess hallucinogenic and/or sympathomimetic properties.



I, R = H
II, R = CH

Experimental Section[4]

1-(2,5-Dimethoxy-4-methylphenyl)-2-nitroethanol.—To a stirred mixture of 3.6 g (20 mmoles) of 2,5-dimethoxy-*p*-tolualdehyde and 2.4 g (40 mmoles) of $MeNO_2$ in 200 ml of EtOH was added a solution of 0.8 g (20 mmoles) of NaOH in 10 ml of H_2O. A precipitation occurred within a few seconds. The mixture was stirred at room temperature for 15 min and then poured into 4 ml of AcOH and 300 g of crushed ice. The resulting mixture was stirred for 1 hr and fluffy yellow crystals contaminated with a brown gummy substance were collected on a filter. The crystals were easily separated from the gummy substance to yield 0.45 g which was recrystallized from *n*-C_6H_{14} giving 0.2 g of needles, mp 91–92°. When the brown gummy substance was washed with 100 ml of hot *n*-C_6H_{14} and filtered, a second crop of 1.3 g of product, mp 89–90°, was obtained. Recrystallization of the second crop of crystals from benzene–C_6H_{14} gave 1.0 g (total yield, 25%), mp 90–91°. *Anal.* ($C_{11}H_{15}NO_5$) C, H, N.

Evaporation of the C_6H_{14}, the mother liquor of the first crop of product, gave 1.7 g of solid (mp 70–75°) which was primarily the unreacted aldehyde.

2,5-Dimethoxy-4-methylphenethanolamine. A mixture of 1.7 g (7 mmoles) of 1-(2,5-dimethoxy-4-methylphenyl)-2-nitroethanol in 25 ml of absolute EtOH and 200 mg of 5% Pd–C catalyst was shaken with H_2 at 2–3 atmosphere for 2.5 hr. The filtered solution was evaporated *in vacuo* leaving 1.4 g (94%) of product, mp 97–100°. Recrystallization from C_6H_6–Et_2O gave 700 mg (47%) of white solid, mp 111–112°. *Anal.* ($C_{11}H_{17}NO_3$) C, H, N.

When the mother liquor was treated with Et_2O–HCl, 300 mg of HCl salt, mp 167–168° was obtained. Recrystallization from EtOH–Et_2O gave 200 mg, mp 171–172°.

2,5-Dimethoxy-4-methylpropiophenone.—To a solution of 15.2 g (0.1 mole) of 2,5-dimethoxytolnene and 9.2 g (0.1 mole) of *n*-C_3H_7COCl in 125 ml of CS_2 was added portionwise 13.4 g (0.1 mole) of $AlCl_3$ at such a rate that the temperature of the reaction mixture remained between 0 and 10°. (The addition required about 30 min.) After stirring at room temperature for 3 hr, the dark green mixture was decomposed by pouring into 80 ml of crushed ice and 5 ml of concentrated HCl and then filtered to yield 3.1 g of solid, mp 76–77°. The filtrate was extracted twice with 50 ml of $CHCl_3$. The $CHCl_3$ extracts were combined, dried (Na_2SO_4), and evaporated *in vacuo* leaving 15.6 g, mp 74–76°, which was recrystallized from 95% EtOH to give 8.4 g, mp 76–77°. Concentration of the mother liquor gave a third crop of 5.6 g, mp 76–77°. The total yield of the reaction was 17.1 g (82%): ir (CCl_4) 5.68 and 5.76 μ (aromatic 1,2,4-substitution); nmr (CCl_4) τ 2.8 (singlet, C_6-H), 3.3 (singlet, C_3-H). *Anal.* ($C_{12}H_{16}O_3$) C, H.

2,5-Dimethoxy-4-methyl-α-isonitrosopropiophenone.—MeONO [prepared from 5.5 g (80 mmoles) of $NaNO_2$ and 4.2 g (100 mmoles) of MeOH by the dropwise addition of 4.0 g (40 mmoles) of H_2SO_4 in 10 ml of H_2O] and HCl gas were bubbled for 1 hr into a solution of 10.4 g (50 mmoles) of 2,5-dimethoxy-4-methylpropiophenone in 200 ml of Et_2O. The addition of HCl was continued for an additional 0.5 hr. During the addition the solution turned red and gradually a precipitation occurred. After stirring overnight at room temperature the precipitate was filtered: yield, 7.5 g of yellow solid, mp 124–128°. The filtrate was extracted 3 times with 25-ml portions of 2 *N* NaOH and the aqueous solution reextracted with 50 ml of Et_2O. The Et_2O extract was dried (Na_2SO_4), and evaporated *in vacuo* giving 3.9 g, mp 130–132°. Both crops of product were combined and recrystallized from benzene to yield 8.9 g (75%) of bright yellow solid, mp 132–134°. *Anal.* ($C_{12}H_{15}NO_4$) C, H, N.

2,5-Dimethoxy-4,α-dimethylphenethanolamine.—A mixture of 4.7 g (20 mmoles) of 2,5-dimethoxy-4-methyl-α-isonitrosopropiophenone, 75 ml of EtOH, 5 ml of concentrated HCl, and 0.5 g of 5% Pd–C catalyst was shaken with H_2 at 2–3 atm until the consumption of H_2 ceased. The filtered solution was evaporated *in vacuo* and the oily residue washed with Et_2O to yield 4.0 g (89%) of solid, mp 233–234°. Recrystallization from EtOH gave 1.4 g, mp 237–238°. Addition of Et_2O to the mother liquor afforded additional 0.6 g of product, mp 236–238°, thereby increasing the yield to 44%. When the first 1.4 g of product was recrystallized once more from EtOH, 0.7 g of solid, mp 247–248°, was yielded. *Anal.* ($C_{12}H_{19}NO_2$·HCl) C, H, N.

A small amount of the HCl salt was converted into the free amine and recrystallized from CCl_4 to give a solid, mp 130–135°.

(1) This work was partially supported by Grants MH-12959 and MH-11168, U. S. Public Health Service, Bethesda, Md.

(2) B. T. Ho, W. M. McIsaac, R. An, L. W. Tansey, K. E. Walker, L. F. Englert, Jr., and M. B. Noel, *J. Med. Chem.*, **13**, 26 (1970).

(3) B. T. Ho, L. W. Tansey, R. L. Balster, R. An, W. M. McIsaac, and R. T. Harris, *ibid.*, **13**, 134 (1970).

(4) Melting points were taken on a Mel-Temp apparatus and are corrected. Where analyses are indicated only by symbols of the elements or functions, analytical results obtained for those elements or functions were within ±0.4% of the theoretical values. Ir spectra of all the compounds were compatible with the assigned structures.

1-Substituted 2,5-Dimethylpyrroles

Laird F. Miller and Ronald E. Bambury

Hess & Clark, Division of Richardson-Merrell, Inc., Ashland, Ohio 44805

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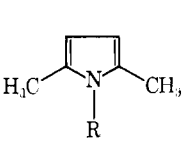
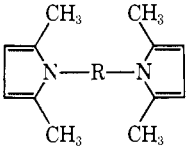
Surprisingly few examples appear in the literature of pyrroles substituted in the 1 position with a heterocyclic nucleus. We wish to report the synthesis of 21 1-heterocyclic substituted 2,5-dimethylpyrroles (Table I). These compounds were tested for chemotherapeutic activity in the following screening programs: *in vitro* and *in vivo* antibacterial, *in vivo* anticoccidial,

TABLE I

1-SUBSTITUTED 2,5-DIMETHYLPYRROLES



1–19



20–21

No.	Starting amine $R(NH_2)_x$; x = 1 or 2	Prep method	Reacn time (hr)	Yield (%)	Formula[d]	Product bp (mm) or mp, °C	Recrystn[m] solvent
1	2-Aminothiazole	I	3	59	$C_9H_{10}N_2S$	78 (0.025)[e]	
2	2-Aminothiazoline	I	8	20	$C_9H_{12}N_2S$	*f*	
3	2-Aminobenzothiazole	I	24	56	$C_{13}H_{12}N_2S$	81–82.5[g]	A
4	2-Amino-5-nitrothiazole	II	52	45	$C_9H_9N_3O_2S$	74–76	B
5	2-Amino-5-(4-nitrophenylsulfonyl)thiazole	II	7	75	$C_{15}H_{13}N_3O_4S_2$	173–175	C
6	2-Amino-4-(4-biphenylyl)thiazole	II	13	42	$C_{21}H_{18}N_2S$	121–123	D
7	2-Aminoimidazole[a,b]	I	31	30	$C_9H_{11}N_3$	191.5–194	E
8	2-Amino-1-methylimidazole[b]	I	9	70	$C_{10}H_{13}N_3 \cdot HCl$	159.5–161.5	E
9	2-Amino-1,3,4-thiadiazole	I	7	60	$C_3H_3N_3S$	96 (0.01)	
10	3-Amino-1,2,4-triazole	I	2	48	$C_3H_{10}N_4$	202–203[h]	F
11	5-Aminotetrazole	I	5.5	56	$C_7H_9N_5$	150–151	C
12	2-Aminopyridine	I	4.5	43	$C_{11}H_{12}N_2 \cdot HCl$	163–164[i]	A
13	2-Amino-3-nitropyridine	II	22	68	$C_{11}H_{11}N_3O_2$	80–82	G
14	2-Amino-5-nitropyridine	I	3	75	$C_{11}H_{11}N_3O_2$	81.5–83	G
15	2-Aminopyrimidine	II	24	55	$C_{10}H_{11}N_3$	84–85 (0.02)[j]	
16	5-Aminouracil	I	1	70	$C_{10}H_{11}N_3O_2$	285–288	H(95:5)
17	2-Amino-4-morpholino-*s*-triazine	I	7.5	25	$C_{13}H_{17}N_5O$	91–92.5	G
18	3-Trifluoromethylaniline	I	1.5	33	$C_{13}H_{12}F_3N$	50–52[k]	H (7:1 at −78°)
19	1-Phenyl-1-(2-pyridyl)hydrazine[c]	I	1.5	73	$C_{17}H_{17}N_3$	64.5–66.5	H (1:1)
20	2,5-Diamino-1,3,4-thiadiazole	I	6.5	35	$C_{14}H_{16}N_4S$	122–124	I
21	2,6-Diaminopyridine	I	6.5	41	$C_{17}H_{19}N_3$	152–156[l]	I

[a] Sulfate. [b] Prepared according to A. G. Beaman, R. Duschinsky, and W. P. Tautz, U. S. Patent 3,287,468 (1966). [c] Prepared according to G. Palazzo and L. Baiocchi [*Ann. Chim.* (Rome), **55**, 935 (1965)]. [d] Compounds (excluding **3**, **10**, **21**) were analyzed for C, H, N and, where applicable, Cl, F, S. All values were within ±0.4% of theoretical. [e] N. P. Buu-Hoï [*J. Chem. Soc.*, 2882 (1949)] reported bp 130–132° (13 mm). [f] Unstable to distillation; purified by preparative glpc. [g] W. S. Bishop [*J. Amer. Chem. Soc.*, **67**, 2261 (1945)] reported mp 79–79.5°. [h] R. Rips, C. Derappe, and N. P. Buu-Hoï [*J. Org. Chem.*, **25**, 390 (1960)] reported mp 203°. [i] Mp 127°, footnote *h*. [j] N. P. Buu-Hoï and N. D. Xuong [*ibid.*, **28**, 850 (1955)] bp 150–151° (12 mm). [k] H. Gilman, C. G. Stuckwisch, and J. F. Nobis [*J. Amer. Chem. Soc.*, **68**, 326 (1946)] reported mp 42°. [l] N. P. Buu-Hoï, R. Rips, and C. Derappe [*Bull. Soc. Chim. Fr.*, 3456 (1965)] reported mp 155°. [m] A, *i*-PrOH; B, Et_2O–hexane (1:1); C, C_6H_6; D, hexane; E, Me_2CO; F, $CHCl_3$; G, petroleum ether (bp 90–100°); H, EtOH–H_2O; I, Et_2O.

and *in vivo* anthelmintic tests. None showed significant biological activity.

Experimental Section

Melting points were taken in open capillary tubes with a calibrated thermometer using a Thomas-Hoover melting point apparatus. The ir and nmr spectra of each compound were consistent with the expected structure. Elemental analyses were performed by Spang Microanalytical Laboratory, Ann Arbor, Mich. Solvents were removed under vacuum on a rotary evaporator. Analytical glpc determinations were carried out with an F & M Model 500 gas chromatograph equipped with a Model 1609 flame ionization dectector. The stainless steel column used was 0.625 × 120 cm packed with 5% SE-30 silicone gum rubber on acid-washed, base-washed, and silanized Anakrom solid support. Preparative glpc separations were accomplished with an F & M Model 776 Prepmaster Jr. using N_2 as the carrier gas. The Al column used was 2.5 × 200 cm and was packed with the same material described above. Unless otherwise indicated, the amines were commercially available.

Compounds Were Prepared by One of Two Methods. Method I.—An equivalent amount of amine hydrochloride and 2,5-hexanedione were refluxed in DMF until glpc analysis showed the disappearance of the dione peak. In most cases H_2O formed during the reaction was removed by using a Dean–Stark water separator filled with molecular sieves. After completion of the reaction, the DMF was poured into a large volume of H_2O and the product was extracted (Et_2O). The ether was dried ($MgSO_4$) and evaporated to give a crude product which was purified by recrystallization or distillation.

Method II.—An equivalent amount of amine (free base) and 2,5-hexanedione were refluxed in an aromatic organic solvent (C_6H_6 or C_6H_5Me) containing a catalytic amount of *p*-toluenesulfonic acid (*p*TsA). The progress of the reaction was followed by the amount of H_2O which collected in a Dean-Stark water separator, or by glpc analysis. After the reaction was complete, the *p*TsA was removed by extraction with aq $NaHCO_3$ solution and the solvent was dried ($MgSO_4$) and evaporated. The crude product was purified by recrystallization or distillation.

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