Notes

Synthesis and Antifungal Properties of Certain 7-Alkylaminopyrazolo[1,5-*a*]pyrimidines[1]

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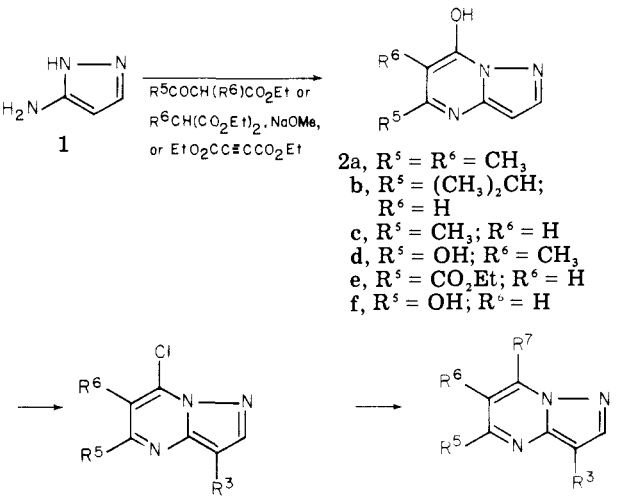
A series of 7-alkylaminopyrazolo[1,5-*a*]pyrimidines (**5–25**) and one 7-alkylthiopyrazolo[1,5-*a*]pyrimidine (**4**) were synthesized from the corresponding 7-chloro precursors **3**, which were prepared in turn from the 7-hydroxy analogues **2**, obtained via condensation of 3-aminopyrazoles with acetoacetate esters, malonate esters, or acetylenedicarboxylate ester. Compounds **4–25** were found to inhibit *Trichophyton mentagrophytes* (in vitro). The degree of inhibition increased with increasing 7-alkylamino chain length up to C_8 units and then began to decrease with longer chain lengths. Unsaturated chains were more fungitoxic than saturated chains, 5-methyl-7-oleylaminopyrazolo[1,5-*a*]pyrimidine [**22**, $R^7 = NH(CH_2)_8CH{=}CH(CH_2)_7CH_3$] being four times more inhibitory and 16 times more fungicidal (against *T. mentagrophytes*) than 5-methyl-7-*n*-octylaminopyrazolo[1,5-*a*]pyrimidine [**11**, $R^7 = NH(CH_2)_7CH_3$]. Although **11** and **22** appeared to have some efficacy as topical antifungal agents, when applied to *T. mentagrophytes* infections in vivo, both caused irritation (of abraded and unabraded guinea pig skin) as did compound **4** (R^5 = Me; $R^7 = SC_8H_{17}$).

Certain 7-alkylaminopyrazolo[1,5-*a*]pyrimidines[1] were synthesized (7-alkoxy and 7-alkylthio derivatives were also prepared but are not being reported here) in a parallel study with some analogous and recently published 7-alkylaminoimidazo[1,2-*a*]pyrimidines[2] in the development of antifungal agents for the topical treatment of dermal *Trichophyton mentagrophytes* infections. Continuing work on the pyrazolo[1,5-*a*]pyrimidines stems from our earlier interests in the design of potential cAMP phosphodiesterase[3] and xanthine oxidase inhibitors,[4] cardiotonic agents,[5] and agents for the inhibition of *Trichomonas foetus*[6] and *Trypanosoma cruzi*.[7]

Chemistry. The general method for preparing the 7-alkylamino- (**5–25**) and 7-alkylthiopyrazolo[1,5-*a*]pyrimidines (**4**) consisted of treating the corresponding 7-chloropyrazolo[1,5-*a*]pyrimidines (**3**) with alkylamines or the sodium salt of an alkyl mercaptan, respectively. The labile 7-chloro substituent was introduced by chlorinating 7-hydroxypyrazolo[1,5-*a*]pyrimidines[8] (**2**) with phosphorus oxychloride.[9] The appropriate derivatives of **2** were synthesized by condensing 3-aminopyrazole[10] (**1**) with (a) ethyl acetoacetate or its derivatives in acetic acid, (b) diethyl malonate or its derivatives in methanolic sodium methoxide, or (c) diethyl acetylenedicarboxylate. For example, the condensation of **1** with ethyl 2-methylacetoacetate gave the 5,6-dimethyl-7-hydroxy heterocycle **2a**, and **1** with diethyl 2-methylmalonate gave the 5,7-dihydroxy-6-methyl analogue **2d**. The condensation of **1** with the acetylenedicarboxylate ester gave the 5-ethoxycarbonyl-7-hydroxypyrazolo[1,5-*a*]pyrimidine (**2e**).[11]

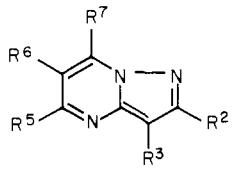
Polyhalogenated pyrazolo[1,5-*a*]pyrimidines were susceptible to nucleophilic displacement only at the 7 position under mild conditions. Thus the 5,7-dichloro heterocycle **3f** could be reacted with *n*-octylamine to give only the 5-chloro-7-*n*-octylamino derivative **14**. The 5-chloro substituent was easily removed by catalytic hydrogenation, giving 7-*n*-octylaminopyrazolo[1,5-*a*]pyrimidine (**12**). Electrophilic bromination in the 3 position was conveniently carried out by treating **3c** with *N*-bromosuccinimide, affording the 3-bromo-7-chloro-5-methylpyrazolo[1,5-*a*]-pyrimidine (**3g**) for example. Halogenation of the 7-alkylamino derivatives **5–7**, **9–21**, and **23–25** generally failed. The syntheses of the newly reported 7-hydroxy (**2**), 7-chloro (**3**), and 7-alkylamino (**5–25**) compounds are given in the Experimental Section and the properties and antifungal activity of **5–25** are listed in Table I. The lone 7-alkylthio derivative, 5-methyl-7-*n*-octylthiopyrazolo-[1,5-*a*]pyrimidine (**4**), is included for comparison with 5-methyl-7-*n*-octylaminopyrazolo[1,5-*a*]pyrimidine (**11**).

Scheme I



Biological Methods. Antimicrobial Activity. The compounds (**4–25**) listed in Table I were assayed for general in vitro antimicrobial activity employing clinical isolates of *Candida albicans* (*C.a.*), *Escherichia coli* (*E.c.*), *Pseudomonas aeruginosa* (*P.a.*), *Staphylococcus aureus* (*S.a.*), *Trichophyton mentagrophytes* (*T.m.*), and *Cryptococcus neoformans* (*C.n.*). Activity in vitro was determined quantitatively by broth dilution assay.[12] Serial dilutions were prepared in chemically defined media in a range from 0.32 to 0.005 μmol/ml. The minimum inhi-

Table I. Antifungal Activity of Certain Pyrazolo[1,5-*a*]pyrimidines against *T. mentagrophytes*



No.	R^7	R^6	R^5	R^3	Emp formula	Mp or bp (mm), °C	MIC/MLC,[a] μmol/ml
4	SC_8H_{17}	H	CH_3	H	$C_{15}H_{23}N_3S$	38-40	0.02/0.16
5	NC_5H_{10}[d]	H	CH_3	H	$C_{12}H_{16}N_4$	78-79	>0.32/>0.32
6	$NHCH_2CO_2H$	H	CH_3	H	$C_9H_{10}N_4O_2$	304-305	>0.32/>0.32
7	$N(C_2H_5)_2$	H	CH_3	H	$C_{11}H_{16}N_4$	204-205	>0.32/>0.32
8	NHC_3H_7	H	CH_3	Br	$C_{10}H_{13}N_4$	93-94	0.08/0.32
9	NHC_6H_{13}	H	CH_3	H	$C_{13}H_{20}N_4$	50-52	0.04/0.32
10	NHC_7H_{15}	H	CH_3	H	$C_{14}H_{22}N_4$	46-47	0.04/0.32
11	NHC_8H_{17}	H	CH_3	H	$C_{15}H_{24}N_4$	48-50	0.02/0.16
12	NHC_8H_{17}[b]	H	H	H	$C_{14}H_{22}N_4 \cdot HCl$	135-136	0.01/0.08
13	NHC_8H_{17}[b]	H	CH_3	H	$C_{15}H_{24}N_4 \cdot HCl$	210-212	0.02/0.16
14	NHC_8H_{17}	H	Cl	H	$C_{14}H_{21}N_4Cl$	34-35	0.02/0.32
15	NHC_8H_{17}	CH_3	Cl	H	$C_{15}H_{23}N_4Cl$	59-61	>0.32/>0.32
16	NHC_8H_{17}	CH_3	CH_3	H	$C_{16}H_{26}N_4$	44-45	0.01/>0.32
17	NHC_8H_{17}	H	$CH(CH_3)_2$	H	$C_{17}H_{27}N_4$	79-80	0.02/>0.32
18	NHC_8H_{17}	H	$CO_2C_2H_5$	H	$C_{17}H_{26}N_4O_2$	70-72	0.32/>0.32
19	NHC_8H_{17}	H	CH_3	$CO_2C_2H_5$	$C_{18}H_{28}N_4O_2$	88-89	0.32/>0.32
20	$NHC_{10}H_{21}$	H	Cl	H	$C_{16}H_{25}N_4Cl$	57-58	>0.32/>0.32
21	$NHC_{10}H_{21}$	H	CH_3	H	$C_{17}H_{28}N_4$	67-68	0.04/>0.32
22	$NH(CH_2)_8CH{=}CH(CH_2)_7CH_3$[c]		CH_3	Br	$C_{25}H_{41}N_4Br$	160-162	0.01/0.02
23	$NH(CH_2)_8CH{=}CH(CH_2)_7CH_3$[c]		CH_3	H	$C_{25}H_{42}N_4$	170 (0.01)	0.005/0.01
24	$NH(CH_2)_3$-c-$N(CH_2CH_2)_2O$[b,c]		CH_3	H	$C_{14}H_{21}N_5 \cdot HCl$	245-247	>0.32/0.32
25	$NHCH_2$(Ph-2,4-Cl_2)[c]		CH_3	H	$C_{14}H_{12}N_4Cl_2$	155-156	0.04/>0.32

[a] MIC = minimal inhibitory concentration; MLC = minimal lethal concentration; range in μmol/ml = 0.32-0.005. [b] Hydrochloride salts. [c] R^6 = H. [d] NC_5H_{10} = piperidino.

bitory concentration (MIC) was recorded as the highest dilution of compound which prevented visible growth of the pathogen. Bacterial and yeast MIC data were read following 24 h of incubation at 35 °C. Dermatophyte inhibition was read after 48 h of incubation at 30 °C.

The in vivo therapeutic effects of the most potent compounds in this study were evaluated using a guinea pig skin infection model.[12] Compounds were formulated in solutions (w/v) of propylene glycol (20%), 70% sorbitol (3%), and ethanol (78%) and in an ointment vehicle of Petrolatum U.S.P. (40%), mineral oil U.S.P. (15%), white beeswax (4.0%), sorbitan sesquioleate (6.0%), water (35%), and sorbic acid (0.2%).

Topical treatment of lesions, caused by two strains of *T. mentagrophytes*, was initiated 3 days postinfection and was continued twice daily for 8 days. Lesions were scored visually for severity. Skin from the lesions was cultured to determine the presence of viable pathogen every other day through the 14th day postinfection. The same treatment regime of abraded and unabraded skin of uninfected guinea pigs was used for topical irritation studies.

Results and Discussion

Minimal inhibitory (MIC) and lethal (MLC) concentrations in vitro are expressed in μmol/ml in Table I. An examination of the MIC/MLC data clearly establishes a structure–activity relationship between the length of the alkylamino chain and the fungistatic–fungicidal properties of the compounds. Antifungal efficacy of saturated nonbranched alkylamino derivatives **9**–**11** and **13** gradually increased to a maximum of eight methylene units (e.g., octylamino). Activity decreased with nine or more carbons (nonylamino, decylamino, etc.). Apparently there was no variation between odd or even numbers of methylene units. This suggests there might be a definite relationship between the length of the alkyl chain, degree of surface activity, and antifungal properties in vitro.

Furthermore, data in Table I suggested that polar or disubstituted alkylamino substituents, e.g., 7-glycinyl (**6**), 7-*N*,*N*-diethylamino (**7**), and 7-(3-*N*-morpholino)propylamino (**24**), were ineffective, having MIC/MLC values greater than 0.32 μmol/ml (regarded as inactive in this study). The substitution of a 5-Cl for a 5-Me decreased the activity. For example, compare **15** (R^5 = Cl; R^6 = Me; R^7 = *n*-$C_8H_{17}NH$) with **16** (R^5 = R^6 = Me; R^7 = *n*-$C_8H_{17}NH$) or **20** (R^5 = Cl; R^7 = *n*-$C_{10}H_{21}NH$) with **21** (R^5 = Me; R^7 = *n*-$C_{10}H_{21}NH$). Additionally, the substitution of a 5-Me for a 5-H also decreased the activity, e.g., **11** (R^5 = Me; R^7 = $C_8H_{17}NH$) was less active than **12** (R^5 = H; R^7 = $C_8H_{17}NH$). The only other groups which were substituted for the 5-H were the 5-isopropyl (**17**) and the 5-ethoxycarbonyl (**18**). It therefore appeared that steric bulk or electronic effects on the pyrazolo [1,5-*a*]pyrimidine ring diminished the basic activity of the more effective derivatives (in vitro). The substitution of other groups for hydrogen was unfavorable not only at the 5 position but also at the 2, 3, or 6 positions as well.

A remarkable improvement in antifungal activity was observed in substituting an unsaturated amine (oleylamino) for the most effective saturated amine (octylamino). A systematic study of multiple conjugated units was not pursued, but the 5-methyl-7-oleylamino [R^7 = $CH_3(CH_2)_7CH{=}CH(CH_2)_8NH$] analogue (**23**) was found to be superior in vitro and in vivo, compared to the corresponding 5-methyl-7-*n*-octylamino (**11**) compound. Bromination in the 3 position of **23**, e.g., **22**, reduced the activity in vitro. The reported antifungal activity of the antibiotic myriocin[13] is apparently related to the presence of a long, unbranched alkyl substituent. The antifungal properties of 2-alkenoic and 2-bromoalkenoic acids have also been correlated with chain length (and pH properties).[14] Sokolova[15] and co-workers have noted a relationship between alkyl chain length and antitubercular properties of a series of 4-alkylamino- and 4-alkylthio-

2,6-dimethylpyrrolo[3,2-*d*]pyrimidines. Perhaps the most interesting parallel between our work (and that of the imidazo[1,2-*a*]pyrimidines[2]) and other published findings is that Noguchi[16] and Ikeda have determined that 3-alkylpyrazoles, especially 3-nonylpyrazole (originally isolated from a natural product, *Houttuynia cordata*), had a broad antifungal spectrum. The antifungal activity against *Trichophyton interdigitale* was directly related to the chain length and degree of surface activity of the 3-alkylpyrazoles. The maximum effectiveness was apparently obtained with the *n*-octyl and *n*-nonyl derivatives and antifungal properties decreased with an increase or decrease in the number of carbon atoms in the chain. It has been observed elsewhere[17] that unsaturated fatty acids are more fungitoxic than saturated fatty acids. The antifungal properties of the polyenes are certainly due to the conjugated system of several olefinic units. Amphotericin B,[18] for example, has seven double bonds.

The more fungicidal compounds in vitro (**11–13** and **23**) were subjected to therapeutic evaluation and skin irritation in vivo. However, when intact or abraded skin of uninfected guinea pigs was treated with these compounds in either vehicle employed (described supra; 1.0% compound w/v in formulation vehicle), erythema and scaling were noted by the sixth day. Compound **23** was more potent in vitro, but also more irritating in vivo, than **11–13**. Vehicle-treated control animals did not show signs of irritation. Topical cures of dermal infections of *T. mentagrophytes* on the guinea pigs were not achieved by formulating **11–13** or **23** at nonirritating concentrations, since no therapeutic effect was observed on comparing these animals with infected, vehicle-only treated control animals. Several 7-alkylthio derivatives were synthesized, but these (**4** is the lone representative of this group presented here for comparison with **11**) compounds were also substantially irritating to the guinea pig skin.

Experimental Section

Melting points were taken in capillary tubes (Thomas-Hoover apparatus) and are uncorrected. All nuclear magnetic resonance spectra (^{1}H NMR) were recorded at 60 MHz on a Hitachi Perkin-Elmer R-20A high-resolution instrument in either Me_2SO-d_6 (DSS standard) or $CDCl_3$ (Me_4Si standard) solution, depending on the solubility of each compound. Infrared (IR) spectra were recorded on a Perkin-Elmer 257 spectrophotometer either in KBr pellets (solids) or NaCl cells (liquids or semisolids). ICN-Woelm neutral, grade I alumina (70–230 mesh) was used for column chromatography. Elemental analyses were performed by Galbraith Labs. of Knoxville, Tenn., and were all within ±0.4% of the theoretical values for C, H, and N.

General Synthesis of 7-Hydroxypyrazolo[1,5-*a*]pyrimidines (2). A. Acetoacetic Ester Condensation. 5,6-Dimethyl-7-hydroxypyrazolo[1,5-*a*]pyrimidine (2a). A mixture of 21.9 g (0.264 mol) of 3-aminopyrazole, 38.0 g (0.264 mol) of ethyl 2-methylacetoacetate, and 80 ml of glacial acetic acid was refluxed for 30 min. A thick white paste resulted, which was filtered and pressed free of acetic acid, then washed with EtOH, and pressed dry with suction to yield 32.0 g (74%) of analytically pure product, mp >300 °C. Anal. ($C_8H_9N_3O$) C, H, N.

Other 5-alkyl-7-hydroxy analogues were prepared in the same manner.

7-Hydroxy-5-isopropylpyrazolo[1,5-*a*]pyrimidine (2b): yield 67–70%; mp 279–281 °C. Anal. ($C_9H_{11}N_3O$) C, H, N. **7-Hydroxy-5-methylpyrazolo[1,5-*a*]pyrimidine (2c)**: prepared as reported by Makisumi.[9]

B. Malonate Ester Synthesis. 5,7-Dihydroxy-6-methylpyrazolo[1,5-*a*]pyrimidine (2d). A mixture of 34.8 g (0.2 mol) of diethyl 2-methylmalonate, 16.6 g (0.2 mol) of 3-aminopyrazole, and 4.6 g of Na metal in 200 ml of absolute ethanol was refluxed for 2 h. The mixture was evaporated in vacuo [40 °C (10 mm)], and the residue was dissolved in 1.2 l. of hot water, and then cooled to room temperature. The solution was acidified (pH 2) with 12 N HCl and the precipitated product was collected by filtration, washed with water, and air-dried: yield 13.5 g (41%); mp >360 °C. Recrystallization from Me_2SO gave an analytical sample. Anal. ($C_7H_7N_3O_2$) C, H, N.

5-Ethoxycarbonyl-7-hydroxypyrazolo[1,5-*a*]pyrimidine (2e) and **7-chloro-5-ethoxycarbonylpyrazolo[1,5-*a*]pyrimidine (3e)** have been reported by Reimlinger and Meryeni[11] and 7-chloro-3-ethoxycarbonyl-5-methylpyrazolo[1,5-*a*]pyrimidine (**3h**) was earlier reported by us.[7]

General Synthesis of 7-Chloropyrazolo[1,5-*a*]pyrimidines. 5,7-Dichloro-6-methylpyrazolo[1,5-*a*]pyrimidine (3d). A mixture of 6.0 g (0.036 mol) of **2d**, 60 ml of phosphorus oxychloride, and 3 g of *N,N'*-dimethylaniline was refluxed for 30–40 min. The dark red solution was evaporated in vacuo [35 °C (10 mm)] and the residual syrup was poured over 100 g of crushed ice and immediately extracted with 5 × 50 ml portions of methylene chloride. The organic extract was washed with cold, saturated sodium carbonate solution and then dried (Na_2SO_4) and evaporated [30 °C (10 mm)]. Chromatography of this syrup with 1:1 benzene-chloroform (neutral alumina) gave 5.0 g (68%) of the product as an ivory-colored solid, mp 63–65 °C. Anal. ($C_7H_5N_3Cl_2$) C, H, N.

7-Chloro-5-methylpyrazolo[1,5-*a*]pyrimidine (3c) was prepared in 80% yield as reported by Makisumi.[9]

5,6-Dimethyl-7-chloropyrazolo[1,5-*a*]pyrimidine (3a) was prepared in a similar manner, omitting the *N,N'*-dimethylaniline: yield 50%; mp 95–95.5 °C. Anal. ($C_8H_8N_3Cl$) C, H, N.

5,7-Dichloropyrazolo[1,5-*a*]pyrimidine (3f) was prepared in 60% yield as reported by us earlier.[7]

3-Bromo-7-chloro-5-methylpyrazolo[1,5-*a*]pyrimidine (3g) was prepared in 67% yield by the method reported by Dorn and Zubek.[19]

General Synthesis of 7-Alkylaminopyrazolo[1,5-*a*]pyrimidines. A. 5-Methyl-7-*n*-octylaminopyrazolo[1,5-*a*]pyrimidine (11). A solution of 11.5 g (0.095 mol) of **3a** in 300 ml of absolute ethanol was treated with 20.5 g (0.19 mol) of *n*-octylamine. The mixture was warmed on a steam bath for 10–15 min, and then the solvent was removed in vacuo [40 °C (10 mm)]. The residue was taken up in 100 ml of methylene chloride, washed with 100 ml of 0.01 N HCl and then 100 ml of water, and then dried (Na_2SO_4) and percolated through an alumina column. The alumina was eluted with more methylene chloride (300 ml) and then ethyl acetate (100 ml). Evaporation of the eluent gave 9.2 g (39%) of product which was recrystallized from acetone–ligroine to give an analytical sample, mp 48–50 °C. Anal. ($C_{15}H_{24}N_4$) C, H, N.

Other 7-alkylamine derivatives were prepared similarly and are listed in Table I.

B. 7-*n*-Octylaminopyrazolo[1,5-*a*]pyrimidine (12) Hydrochloride. A solution of 700 mg (2.5 mmol) of 5-chloro-7-*n*-octylaminopyrazolo[1,5-*a*]pyrimidine (**14**, prepared from 5,7-dichloropyrazolo[1,5-*a*]pyrimidine[7]) in 100 ml of ethanol containing 205 mg (2.5 mmol) of sodium acetate was hydrogenated with 0.5 g of 10% palladium-on-charcoal catalyst at 40 psi for 1–2 h. After an uptake of the theoretical amount of hydrogen, the catalyst was removed by filtration and the solvent was evaporated. The residue was extracted with 50 ml of methylene chloride and this solution was chromatographed on neutral alumina and eluted with more methylene chloride. Evaporation of the eluent gave an oil which was dissolved in dry ether and saturated with dry hydrogen chloride. The hydrochloride salt of the product precipitated and was recrystallized from acetone or methanol–ether: yield 375 mg (55%); mp 145–146 °C. Anal. ($C_{13}H_{22}H_4$·HCl) C, H, N.

5-Methyl-7-*n*-octylthiopyrazolo[1,5-*a*]pyrimidine (4). A solution of sodium octyl mercaptan was prepared in situ from 0.35 g (15 mmol) of sodium in 10 ml of methanol and 2.8 g (20 mmol) of *n*-octyl mercaptan. The solution was warmed briefly at 50 °C (steam bath) and 1.0 g (6 mmol) of **3a** was added. The mixture was heated at 75 °C for 20 min, then cooled to room temperature, filtered, and evaporated in vacuo [40 °C (15 mm)]. The residual oil thus obtained was partitioned between water and methylene chloride, and the organic layer was separated (separatory funnel), dried (Na_2SO_4), and chromatographed on neutral alumina with more methylene chloride. Evaporation of the eluent gave 700 mg (42%) of a white solid, recrystallized from ligroine as white plates,

mp 38–40 °C. Anal. ($C_{15}H_{23}N_3S$) C, H, N.

Acknowledgment. The authors thank Dr. K. Senga, Dr. D. E. O'Brien, and Mr. R. H. Springer for helpful suggestions. We also thank Ms. P. F. Dougherty and Mr. D. W. Yotter for determining antimicrobrial data and Mrs. M. Alta and Mr. E. Banta for providing spectra and analytical data.

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Lipophilicity and Serotonin Agonist Activity in a Series of 4-Substituted Mescaline Analogues

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Replacement of the 4-methoxy of mescaline with higher alkyl homologues or with bromine led to increased activity at serotonin receptors in a sheep umbilical artery preparation. This activity appears correlated with lipophilicity, as measured by 1-octanol–water partition coefficients, but drops off when the 4-substituent is about five atoms in length. It is suggested that 3,4,5-trisubstitution may give compounds which are as active as those with the 2,4,-5-substitution pattern.

Barfknecht et al.[1] recently reported that a correlation exists between 1-octanol–water partition coefficients and human activity for a series of psychotomimetic phenylisopropylamines. Optimum lipophilicity was reported to be at log $P = 3.14$, a value close to the log P of 2.96 for LSD (W. J. Dunn, III, personal communication). In that study, however, the value of log P estimated for mescaline appeared to place it outside of the range where activity would be expected, and it was suggested that some other parameter was able to compensate for the low lipophilicity.

In an early study of a series of phenethylamines it was shown that in animals the loss of the 5-methoxy from mescaline resulted in reduced activity, while loss of the 4-methoxy abolished activity completely.[2] In humans 3,4-dimethoxyphenethylamine is nonhallucinogenic.[3] Substitution of the 4-methoxy with a benzyloxy[2] or an ethoxy[4] was reported to increase activity. Replacement of the 4-methoxy with a methyl also gives a compound which retains activity.[5] In view of these reports it was decided to examine the possibility that such modifications of the 4-substituent might lead to increased potency as a result of changes in lipophilicity. Although the nature of the 4-substituent has been shown to be important for maximum activity, compounds with a relatively long lipophilic chain at this position show high activity in humans.[6]

This report describes a series of compounds, **3a–f** (Table II), for which 1-octanol–water partition behavior was examined and was related to activity at serotonin receptors in the sheep umbilical artery preparation.[7] This model previously has been shown to have a promising correlation with hallucinogenic activity in man.[7,8]

Chemistry. The phenylacetonitriles, **2a–f**, served as useful intermediates in the synthetic scheme. With the exception of compound **2f**, all were prepared by alkylation of 3,5-dimethoxy-4-hydroxyphenylacetonitrile, obtained in an overall yield of 59% from 2,6-dimethoxyphenol using the method of Short et al.[12] The yields of most alkylations were excellent to good (see Table I), in spite of anticipated steric problems. Reduction of compounds **2a–d** was accomplished catalytically with hydrogen, and compounds **3e,f** were obtained by borohydride–cobalt reduction according to the method of Satoh et al.[13] This latter method appeared to give small amounts of O-debenzylation but