2,4-Dimethyl Derivatives of 5-Methoxy-3-indolylethylamines. New 5-Oxygenated Tryptamines

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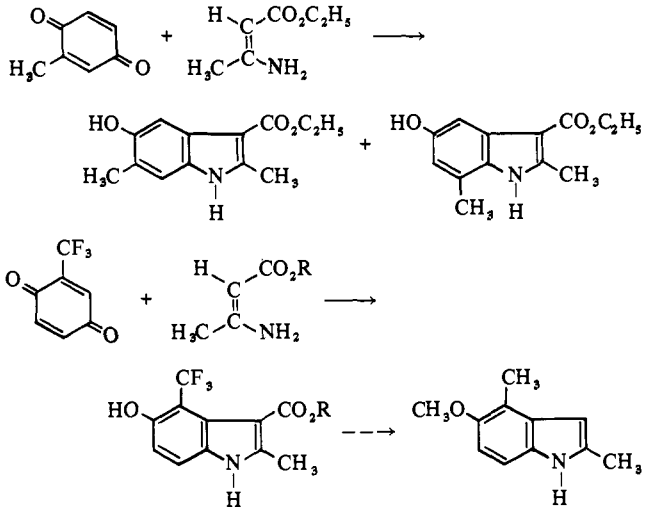
Our investigations of the Nenitzescu 5-hydroxyindole synthesis have resulted in procedures for the preparation of reasonable quantities of 4-, 6-, and 7-methyl derivatives of 5-methoxy-2-methylindole. Thus, reaction of toluquinone with ethyl 3-aminocrotonate gives the precursors for the 6- and 7-methyl derivatives in essentially equivalent yield (Scheme I).[1] Although the corresponding **4**-methyl derivative is not formed in this condensation,[1,2] the reaction of alkyl 3-aminocrotonates with 2-trifluoromethyl-1,4-benzoquinone provides a convenient entry into the 4-methyl series, for alkyl 5-hydroxy-4-trifluoromethylindole-3-carboxylates result in excellent yield.[3] Decarboxylation of the product derived from *tert*-butyl 3-aminocrotonate and subsequent methylation gave 5-methoxy-2-methyl-4-trifluoromethylindole which on reduction with lithium aluminum hydride afforded 5-methoxy-2,4-dimethylindole (**1**).

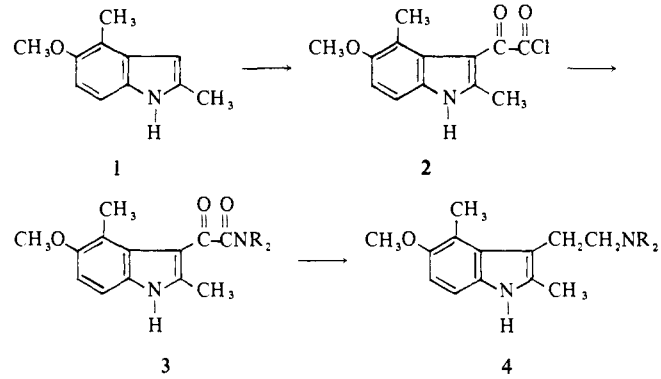
Scheme I



The availability of these new indoles prompted us to prepare certain 5-methoxy-2,4(6 or 7)-dimethyltryptamines. In the present report the synthesis of 2,4-dimethyl derivatives and their effects on the central nervous system are described. An accompanying paper reports the preparation and biological properties of the 2,6- and 2,7-dimethyl derivatives.[4]

The desired compounds were prepared by application to **1** of the tryptamine synthesis of Speeter and Anthony.[5] Thus indole **1** reacted with oxalyl chloride to give 76% of the 3-indolylglyoxalyl chloride **2** (Scheme II). Treatment of this acyl halide with the appropriate amine gave the 3-indolylglyoxamides of Table I. Reduction of these glyoxamides with lithium aluminum hydride produced the tryptamines of Table II in the expected fashion.[5]

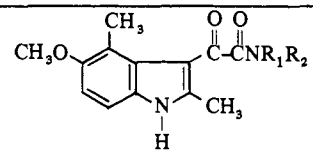
Scheme II



Biology. Representative compounds were tested for their ability to induce ataxia, to decrease locomotor activity, and to afford protection against electroshock-induced and strychnine-induced convulsions in mice. The data for the more active compounds are given in Table III; comparable results for the clinically accepted 7-chloro-1-methyl-5-phenyl-1,3-dihydro-2*H*-1,4-benzodiazepin-2-one (**5**)[6] and 1-(5,6-dimethoxy-2-methylindolyl-3-ethyl)-4-phenylpiperazine (**6**)[7] are included. Tryptamines **4e–g** and **4i** failed to meet the minimum criteria for acceptance in these tests, and data for these compounds are not given.

The other 5-methoxy-2,4-dimethyltryptamines have interesting effects on the central nervous system as judged by these procedures. This property distinguishes the 4-methyl derivatives from the corresponding 5-methoxy-2,6(or 7)-dimethyltryptamines which are of little interest in these tests.[4] Compounds **4a** and **4b** have a spectrum of activity in mice similar to that of the benzo-1,4-diazepine **5** which is clearly more potent. Compounds **4h** and **4j** are congeners of **6**. The limited data suggest a similar profile of activity and potency for these compounds even though the 4-methyl

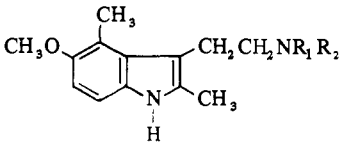
Table I. 5-Methoxy-2,4-dimethyl-3-indolylglyoxamides



No.	NR_1R_2	Yield,[a] %	Recrystn solvent	Mp, °C	Formula	Analyses
3a	$N(CH_3)_2$	43	Acetone–hexane	149–150	$C_{15}H_{18}N_2O_3$	C, H, N
3b	Δ^3-Pyrrolino	35	MeOH–ether	164–167	$C_{17}H_{18}N_2O_3$	C, H, N
3c	$NHCH_2C(CH_3)=CH_2$	39	Acetone–petroleum ether	206–208	$C_{17}H_{20}N_2O_3$	C, H, N
3d	Pyrrolidino	53	Acetone–hexane	174–177	$C_{17}H_{20}N_2O_3$	C, H, N
3e	Morpholino	54	Acetone–petroleum ether	151–153	$C_{17}H_{20}N_2O_4$	C, H, N
3f	$N(C_3H_7)_2$	57	Acetone–petroleum ether	159–161	$C_{19}H_{26}N_2O_3 \cdot 0.5H_2O$	C, H, N, H_2O[b]
3g	3-Azabicyclo[3.2.2]nonane	30	Acetone–hexane	232–234	$C_{21}H_{26}N_2O_3$	C, H, N
3h	4-Phenyl-1-piperazinyl	89	Acetone–ether	147–149	$C_{23}H_{25}N_3O_3$	C, H, N
3i	4-Phenylpiperidino	52	MeOH–H_2O	165–167	$C_{24}H_{26}N_2O_3$	C, H, N

[a] Overall for two stages from 5-methoxy-2,4-dimethylindole. [b] Determined by Karl-Fischer analysis.

Table II. 5-Methoxy-2,4-dimethyltryptamines



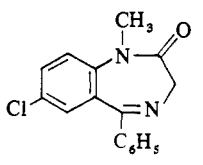
No.	NR_1R_2	Yield, %	Recrystn solvent	Mp, °C	Formula	Analyses
4a	$N(CH_3)_2$	23	Acetone–ether	133–135	$C_{15}H_{22}N_2O \cdot C_4H_6O_4$[a]	C, H, N
4b	Δ^3-Pyrrolino	53	Ether	127–129	$C_{17}H_{22}N_2O$	C, H, N
4c	$NHCH_2C(CH_3)=CH_2$	21	Acetone–ether	167–169	$C_{17}H_{24}N_2O \cdot C_4H_6O_4$[a]	C, H, N
4d	Pyrrolidino	77	Acetone–ether	120–122	$C_{17}H_{24}N_2O$	C, H; N[b]
4e	Morpholino	73	Ether–petroleum ether	126–128	$C_{17}H_{24}N_2O_2$	C, H, N
4f	$N(C_3H_7)_2$	69	EtOH	170–172	$C_{19}H_{30}N_2O \cdot C_4H_6O_4$[a]	C, H, N
4g	3-Azabicyclo[3.2.2]nonane	67	Acetone	183–184	$C_{21}H_{30}N_2O \cdot C_4H_6O_4$[a]	C, H, N
4h	4-Phenyl-1-piperazinyl	51	*i*-PrOH	260–263	$C_{23}H_{29}N_3O \cdot HCl \cdot 0.75H_2O$	C, H, N, Cl, H_2O[c]
4i	4-Phenylpiperidino	43	Ether–petroleum ether	190–193	$C_{24}H_{30}N_2O$	C, H, N,
4j	4-(*o*-Methoxyphenyl)-1-piperazinyl	11[d]	*i*-PrOH	228–231	$C_{24}H_{31}N_3O_2 \cdot HCl \cdot 0.5H_2O$	C, H, N, Cl, H_2O[c]

[a]Succinate salt. [b]N: calcd, 10.28; found, 9.44. [c]Determined by Karl–Fischer analysis. [d]Overall yield from 5-methoxy-2,4-dimethylindole.

Table III. Biological Activities of Representative 5-Methoxy-2,4-dimethyltryptamines and Selected Reference Agents

		Median effective dose, mg/kg ip				
No.		Ataxia[a]	Motor act. decrease[b]	Antielectroshock[c]	Antistrych.[d]	Lethality[e]
4a	3-(2-Dimethylaminoethyl)-5-methoxy-2,4-dimethylindole succinate	30 (13–64)	21	44 (32–60)	50[f]	>112 (0)
4b	5-Methoxy-2,4-dimethyl-3-[2-(3-pyrrolin-1-yl)ethyl]indole	50 (30–65)	14		35 (17–69)	200 (50)
4c	5-Methoxy-2,4-dimethyl-3-[2-(2-methylallylamino)ethyl]indole succinate	76 (51–113)		37 (26–52)		304 (70)
4d	5-Methoxy-2,4-dimethyl-3-[2-(1-pyrrolidinyl)ethyl]indole	64 (44–93)	39	46 (27–78)		232 (70)
4h	5-Methoxy-2,4-dimethyl-3-[2-(4-phenyl-1-piperazinyl)ethyl]indole hydrochloride		7			>70 (0)
4j	5-Methoxy-3-[2-[4-(*o*-methoxyphenyl)-1-piperazinyl]ethyl]-2,4-dimethylindole dihydrochloride	18 (13–25)	5.6		>10	100 (50)
5	7-Chloro-1-methyl-5-phenyl-1,3-dihydro-2*H*-1,4-benzodiazepin-2-one	8 (3–24)	9	11 (8–17)	3 (3–4)	>800 (20)
6	5,6-Dimethoxy-2-methyl-3-[2-(4-phenyl-1-piperazinyl)ethyl]indole	34 (15–78)	3.4			>250 (0)

[a]Determined as described by W. B. Wright, Jr., H. J. Brabander, R. A. Hardy, Jr., and A. C. Osterberg, *J. Med. Chem.*, 9, 852 (1966); 95% confidence limits are given in parentheses. Absence of figures signifies no effect at 100 mg/kg. [b]Determined as described by Wright, *et al.*, *ibid.*, 9, 852 (1966); the cited value is the estimated dose where motor activity is depressed by 50% as measured in one group of five mice at each of at least three dose levels. The lack of a figure indicates no effect at 50 mg/kg. [c]Determined as described by E. A. Swinyard, W. C. Brown, and L. S. Goodman, *J. Pharmacol. Exp. Ther.*, 106, 319 (1952); the lack of a figure indicates no effect at 50 mg/kg. [d]Determined by a modification of the method of H. M. Hanson and C. A. Stone, "Animal and Clinical Pharmacological Techniques in Drug Evaluation," Vol. I, J. H. Nodine and P. E. Siegler, Ed., Yearbook Medical Publishers, Chicago, Ill., 1964, p 317; no entry indicates lack of an effect at 50 mg/kg. [e]The figure in parentheses gives the percentage of ten mice affected at highest test dose. [f]Estimated (50% inhibition at 50 mg/kg, not tested at higher doses).



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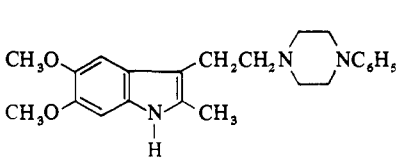

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derivatives lack the 6-oxygenated function previously believed to be necessary for good activity in this series.[7b]

Experimental Section

Melting points were determined in open capillary tubes on a Mel-Temp apparatus and are uncorrected. Ultraviolet spectra were determined in methanol solution with a Cary recording spectrophotometer, and infrared spectra were determined in potassium bromide disks with a Perkin-Elmer Model 21 spectrophotometer. Proton magnetic resonance spectra were determined with a Varian A-60D spectrometer in the indicated solvent using tetramethylsilane as an internal standard. Evaporations were carried out under reduced pressure.

5-Methoxy-2,4-dimethyl-3-indoleglyoxyloyl Chloride. A solution of 1.50 ml (17.8 mmol) of oxalyl chloride in 20 ml of anhydrous ether was added over 10 min to a stirred solution of 2.69 g (15.4 mmol) of 5-methoxy-2,4-dimethylindole (**1**) in 40 ml of ether at 0°. The mixture was stirred an additional 15 min and then slowly diluted by the addition of 150 ml of petroleum ether at 0°. Filtration afforded 3.10 g (76%) of product. The tan solid was used without purification for the preparation of the glyoxamides.

Preparation of the 5-Methoxy-2,4-dimethylindolyl-3-glyoxamides. The following preparation of 4-(5-methoxy-2,4-dimethylindolyl-3-glyoxyloyl)morpholine (**3e**) illustrates the general procedure. A solution of 5.00 ml (57.5 mmol) of morpholine in 20 ml of anhydrous ether was added dropwise to a stirred solution of 3.10 g (11.6 mmol) of 5-methoxy-2,4-dimethyl-3-indoleglyoxyloyl chloride in 250 ml of ether at 0°. The mixture was stirred at 0° for 1 hr and the yellow solid was then collected by filtration to yield 2.62 g (71%) of solid, mp 149–150°. The characterization of this substance and other indolyl-3-glyoxamides is given in Table I.

Preparation of the 5-Methoxy-2,4-dimethyl-3-indolylethylamines (4). The following experiment illustrates the general procedure. A solution of 1.00 g (3.16 mmol) of (5-methoxy-2,4-dimethyl-3-indolyl)glyoxyloylmorpholine in 50 ml of anhydrous tetrahydrofuran was stirred at 0° under argon while 1.00 g (26.4 mmol)

of lithium aluminum hydride was cautiously added. The mixture was stirred at room temperature for 16 hr, and the excess hydride was decomposed by the dropwise addition of 6.5 ml of saturated aqueous sodium potassium tartarate solution. The solid was collected by filtration and washed with 50 ml of ethyl acetate. The combined filtrate and washings were dried over anhydrous magnesium sulfate and concentrated *in vacuo*. Crystallization of the residue from ether–petroleum ether yielded 669 mg (73%) of 5-methoxy-2,4-dimethyl-3-(2-morpholinoethyl)indole, mp 126–128°. The characterization of this substance is given in Table II.

Acknowledgment. The authors are indebted to Messrs. Brancone and Fulmor and their staffs for the microanalyses and spectral data, respectively.

References

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(6) L. H. Sternbach and E. Reeder, *J. Org. Chem.*, **26**, 4936 (1961).
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Glutaryl-*S*-(*p*-bromobenzyl)-L-cysteinylglycine. A Metabolically Stable Inhibitor of Glyoxalase I†

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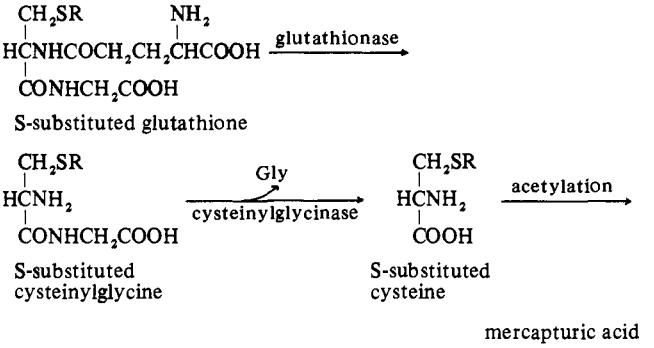
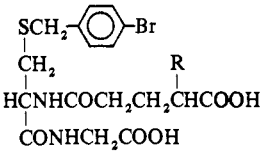
The antineoplastic action of α-ketoaldehydes, including methylglyoxal, has been well documented.[1-3] However, these agents are rapidly metabolized to the corresponding inactive α-hydroxy acids by the glyoxalase enzyme system.[4] These observations prompted our previous suggestion that an appropriate glyoxalase inhibitor in combination with a ketoaldehyde may be an effective means of chemotherapy.[5] Since reduced glutathione is a cofactor in the glyoxalase reaction, S-substituted glutathione derivatives were found to be effective inhibitors of glyoxalase I obtained from yeast.[4-6] Some of these inhibitors exhibited cytotoxic activity against L1210 leukemia and KB cells in tissue culture and also increased the toxicity of methylglyoxal in L1210 cells.[5] The rapid metabolism of S-substituted glutathione derivatives by glutathionase in the mouse rendered these inhibitors inactive when tested *in vivo*.

Glutathione and its S-substituted derivatives are known to be rapidly hydrolyzed in animals by two enzymes, glutathionase (γ-glutamyl transpeptidase) and cysteinylglycinase.[7-9] Glutathionase is responsible for releasing an S-substituted cysteinylglycine from a glutathione derivative; cysteinylglycinase further degrades the cysteinylglycine derivative so formed as illustrated by the degradation of an S-substituted glutathione in Scheme I.

Scheme I. Metabolic Degradation of Glutathione Derivatives



In view of these observations, it became desirable to design a glyoxalase inhibitor that would resist the rapid degradation by the glutathionase enzymes. Compound **1** represents a tripeptide analog of the previously tested *S*-*p*-bromobenzylglutathione (**2a**) in which the γ-glutamyl moiety is replaced by a glutaryl group. The rationale for selecting **1**

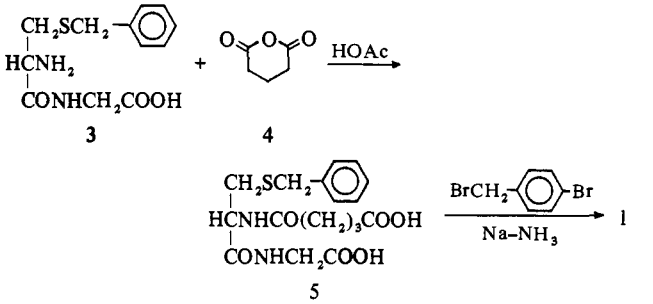


1, R = H
2a, R = NH_2
2b, R = NHAc

was based on the fact that the glutathione derivative **2a** was the most potent inhibitor of yeast glyoxalase I in a series of 40 compounds tested.[6] In addition, the lack of an absolute requirement for the free α-amino group was evidenced by the potent, but decreased, inhibitory activity of the N-acetylated derivative **2b**.[6] Thus, replacement of the α-amine by a hydrogen should result in a glyoxalase inhibitor that cannot be recognized as a γ-glutamyl peptide by the glutathionase enzyme.

Chemistry. *S*-Benzyl-L-cysteinylglycine (**3**)[10] was condensed with glutaric anhydride (**4**) in glacial acetic acid (Scheme II) and gave glutaryl-*S*-benzyl-L-cysteinylglycine

Scheme II



(**5**) in good yield. Removal of the benzyl group from **5** followed by condensation with *p*-bromobenzyl bromide in liquid ammonia and sodium gave the desired product **1**.

Biological Results. The inhibitor concentrations required for 50% inhibition of the glyoxalase I reaction, using 1.25 m*M* methylglyoxal and 0.217 m*M* glutathione as substrates, are summarized in Table I. The tenfold increase in inhibition by the *p*-bromo analog **1** compared with the benzyl derivative **5** is consistent with our previous observation[6] with glutathione derivatives that a *p*-bromo group greatly enhances binding to the enzyme. The inactivity of S-substituted cysteinylglycines such as **3** illustrates the contribu-

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