3-Alkyl-1,3-thiazane Derivatives and Precursors as Antiradiation Agents[1]

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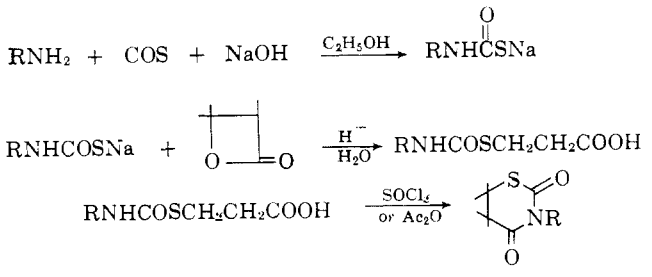
3-Alkyl-1,3-thiazane-2,4-diones and 3-alkyl-1,3-thiazane-2-thione-4-ones were prepared as potential protective agents against ionizing radiation. These compounds were prepared by the ring closure of β-alkylcarbamoylmercaptopropionic acids and β-alkylthiocarbamoylmercaptopropionic acids. The assignment of the structures was supported by n.m.r. spectra. The compounds were found to be inactive in radiation protection tests. Some of the compounds were also tested for nematocidal activity but were found to be inactive.

3-(β-Aminoethyl)-1,3-thiazane-2,4-dione hydrochloride was reported to have antiradiation activity.[2] We have also found that 1,3-thiazane-2,4-dione itself possessed some activity. These observations made it desirable to synthesize and test a series of 3-alkyl-1,3-thiazane-2,4-diones and 3-alkyl-1,3-thiazane-2-thione-4-ones as potential antiradiation compounds.

Substituted 1,3-thiazane-2,4-diones and 1,3-thiazane-4-one derivatives have been patented as useful sedatives, hypnotics, intravenous anesthetics, or anticonvulsants by Gash and Wheeler.[3] Since certain thiazolidinediones are known for their sedative and antispasmodic actions, Vladzimirskaya[4] prepared 3-aryl-1,3-thiazane-2,4-diones as possible sedatives and antispasmodics but did not report biological results. Rhodanine, its derivatives, and thiazolidinedione derivatives are very well known for their varied biological activities.[5] Hence the compounds prepared during the present investigation might also be interesting in a variety of biological tests.

Attempts to N-alkylate 1,3-thiazane-2,4-dione by reacting 1,3-thiazane-2,4-dione, sodium or lithium hydride, and alkyl halides using dimethylformamide or toluene as a solvent did not furnish the desired compound. In all cases 1,3-thiazane-2,4-dione was recovered. Hence 1,3-thiazane-2,4-diones were prepared according to the following scheme.



Similarly 3-alkyl-1,3-thiazane-2-thione-4-ones were prepared by using carbon disulfide instead of carbon oxysulfide in the reaction with amines.

β-Alkylthiocarbamoylmercaptopropionic acids showed the C–N stretch at 6.5 to 6.7 μ in the infrared spectra which is the characteristic absorption for dithiocarbamates.[6] The infrared spectra of β-alkylcarbamoylmercaptopropionic acids also showed this characteristic absorption at 6.5 to 6.7 μ.

β-(2-Diethylaminoethylthiocarbamoyl)mercaptopropionic acid and β-(3-diethylaminopropylthiocarbamoyl)mercaptopropionic acid were obtained as a dihydrate and a monohydrate, respectively. It was expected that both these propionic acids should have zwitterionic structures. Surprisingly, β-(2-diethylaminoethylthiocarbamoyl)mercaptopropionic acid dihydrate showed unionized carboxyl carbonyl absorption at 5.83 μ in the infrared spectrum, indicating a nonzwitterionic structure. As expected, β-(3-diethylaminopropylthiocarbamoyl)mercaptopropionic acid hydrate showed the absence of unionized carboxyl carbonyl absorption at 5.8–5.9 μ and the presence of ionized carboxyl carbonyl absorption at 6.36 μ, indicating the zwitterionic structure in this case. The assignment of zwitterionic structure by infrared analysis is supported by the work of Goodman, Ross, and Baker[7a] and Oliver, Dann, and Gates,[7b] who characterized zwitterions of certain thiazolidine and thiazane derivatives. When both acids were heated at 80° for 20 hr. at 0.5 mm., they lost water of crystallization. Hence the hydrated structures of these acids were assigned on the basis of analytical results, loss of water on heating, and infrared spectra.

3-Alkyl-1,3-thiazane-2-thione-4-ones have been generally prepared by the ring closure of β-alkylthiocarbamoylmercaptopropionic acids with acetic anhydride using a small amount of concentrated sulfuric acid. However, when β-*n*-butylcarbamoylmercaptopropionic acid was treated with acetic anhydride to effect cyclization, β-N-(*n*-butyl)-N-acetylcarbamoylmercaptopropionic acid was obtained. Therefore most of the β-alkylcarbamoylmercaptopropionic acids were cyclized to their corresponding thiazanediones by using thionyl chloride.

The n.m.r. spectra of 3-*n*-propyl-1,3-thiazane-2-thione-4-one and 3-allyl-1,3-thiazane-2-thione-4-one were in accord with the assigned structures, in particular showing a singlet resonance due to the four (accidently equivalent) ring protons at 6.87 τ. Characteristic multiplets from the N-*n*-propyl and N-allyl groups are present at approximately 8 τ, but the N-methylene resonance occurred at surprisingly low field (about 5.0–5.7 τ). This is apparently typical for N-

(1) Contribution No. 1165 from the Department of Chemistry, Indiana University, Bloomington, Indiana. This investigation was supported by the U. S. Army Medical Research and Development Command, Department of the Army, under contract No. DA-49-193-MD 2096.

(2) E. Campaigne and M. C. Wani, Abstracts, 139th National Meeting of the American Chemical Society, St. Louis, Mo., March, 1961.

(3) V. W. Gash and K. W. Wheeler, U. S. Patent 2,585,064 (Feb. 12, 1952); *Chem. Abstr.*, **46**, 7593 (1952); U. S. Patent 2,697,500 (May 25, 1954), *Chem. Abstr.*, **49**, 4727 (1955).

(4) E. V. Vladzimirskaya, *J. Gen. Chem. USSR*, **32**, 528 (1962).

(5) F. C. Brown, *Chem. Rev.*, **61**, 463 (1961).

(6) L. J. Bellamy, "Infrared Spectra of Complex Molecules," 2nd Ed., Methuen, London, 1960, p. 357.

(7) (a) L. Goodman, L. O. Ross, and B. R. Baker, *J. Org. Chem.*, **23**, 1951 (1958); (b) G. L. Oliver, J. R. Dann, and J. W. Gates, *J. Am. Chem. Soc.*, **80**, 702 (1958).

TABLE I

β-ALKYLTHIOCARBAMOYLMERCAPTOPROPIONIC ACIDS, $RNHCSSCH_2CH_2COOH$

R	M.p., °C.[a]	% yield	Formula	% sulfur Calcd.	% sulfur Found	% nitrogen Calcd.	% nitrogen Found
CH_3	87.5–88.0	53	$C_5H_9NO_2S_2$	[b]			
C_2H_5	98.0–98.5	21	$C_6H_{11}NO_2S_2$	[c]			
n-C_3H_7	78.5–79.0	32	$C_7H_{13}NO_2S_2$	[b]			
n-C_4H_9	83.0–83.5	34	$C_8H_{15}NO_2S_2$	[b]			
n-C_6H_{13}	75.0–76.5	35	$C_{10}H_{19}NO_2S_2$	[d]			
$OH(CH_2)_2$	93.5–94.0	10	$C_6H_{11}NO_3S_2$	30.62	30.56	6.70	6.93
$CH_3O(CH_2)_2$	113.0–113.5	81	$C_7H_{13}NO_3S_2$	28.30	28.69	6.28	6.31
$CH_2CH{=}CH_2$	69.7–70.0	29	$C_7H_{11}NO_2S_2$	[e]			
$(C_2H_5)_2N(CH_2)_2$[f]	110.0–111.0	12	$C_{10}H_{24}N_2O_4S_2$	21.33	20.98	9.30	9.40
$(C_2H_5)_2N(CH_2)_3$[g]	109.0–109.5	14	$C_{11}H_{24}N_2O_3S_2$	21.62	22.06	9.45	9.29
o-$CH_3OC_6H_4$	117.0–117.5	56	$C_{11}H_{13}NO_3S_2$	23.61	23.34	5.17	5.20

[a] All the melting points are corrected. [b] J. L. Garraway, *J. Chem. Soc.*, 4072 (1962), reports m.p.: CH_3, 85–86.5°; n-C_3H_7, 75–76°; n-C_4H_9, 83–84°. [c] T. L. Gresham, J. E. Jansen, and F. W. Shaver, *J. Am. Chem. Soc.*, **70**, 1001 (1948), report m.p. 97–98°. [d] *Anal.* Calcd.: C, 48.19; H, 7.63. Found: C, 48.11; H, 7.54. [e] *Anal.* Calcd.: C, 40.97; H, 5.37. Found: C, 41.02; H, 5.59. [f] *Anal.* Calcd.: C, 39.97; H, 8.00. Found: C, 40.32; H, 7.27. [g] *Anal.* Calcd. hydrate (zwitterionic): C, 44.6; H, 8.11. Found; C, 4.50; H, 8.31.

TABLE II

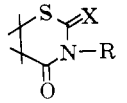
β-ALKYLCARBAMOYLMERCAPTOPROPIONIC ACIDS $RR_1NCOSCH_2CH_2COOH$[a]

R	R_1	M.p., °C.[b]	% yield	Formula	% sulfur Calcd.	% sulfur Found	% nitrogen Calcd.	% nitrogen Found
CH_3	H	87.5	55.2	$C_5H_9NO_3S$	19.63	19.56	8.52	8.58
C_2H_5	H	100.5	27.1	$C_6H_{11}NO_3S$	18.10	18.30	7.91	7.75
n-C_3H_7	H	117–117.5	27.2	$C_7H_{13}NO_3S$	16.75	16.59	7.32	7.36
n-C_4H_9[c]	H	106	77	$C_8H_{15}NO_3S$	15.60	15.42	6.83	6.77
n-C_6H_{13}	H	106.5	51	$C_{10}H_{19}NO_3S$	13.73	13.85	6.00	6.20
n-C_4H_9	$COCH_3$	128–130 (0.5 mm.)[d]	46.3	$C_{10}H_{17}NO_4S$	12.95	12.74	5.66	5.16
$H_3CO(CH_2)_2$	H	59.8	77.2	$C_7H_{13}NO_4S$	15.45	15.09	6.76	6.74
o-$OCH_3C_6H_4$[f]	H	122	41.5	$C_{11}H_{13}NO_4S$	12.54	12.44	[e]	
$CH_2{=}CHCH_2$	H	101	26.0	$C_7H_{11}NO_3S$	[g]			

[a] Colorless plates or needles from benzene. [b] All melting points corrected. [c] J. E. Jansen, U. S. Patent, 2,602,813 (July 8, 1952); *Chem. Abstr.*, **47**, 7536 (1953). [d] B.p.; $n^{28}D$ 1.475. [e] *Anal.* Calcd.: C, 51.76; H, 5.09. Found: C, 51.98; H, 4.92. [f] Violet needles from benzene. [g] Equiv. wt. calcd., 189.00; found, 189.00; Langlet, *Öf. Sv.*, 165 (1892) (Beilstein, IV, 391), reports m.p. 103°.

TABLE III

3-ALKYL-1,3-THIAZANE-2,4-DIONES AND 3-ALKYL-1,3-THIAZANE-2-THIONE-4-ONES



R	X	M.p.,[a] or b.p., °C. (mm.)	% yield	$n^{22}D$	Formula	% sulfur Calcd.	% sulfur Found	% nitrogen Calcd.	% nitrogen Found
CH_3	O	44.0–44.5	40		$C_5H_7NO_2S$	22.06	21.76	9.64	9.43
C_2H_5	O	118–120 (1)	41	1.6368	$C_6H_9NO_2S$	[b]			
n-C_3H_7	O	110–111 (0.4)	63	1.5260[c]	$C_7H_{11}NO_2S$	18.50	18.47	8.09	7.61
n-C_4H_9	O	120–121 (0.5)	40	1.5170[c]	$C_8H_{13}NO_2S$	17.11	17.46	7.45	7.11
n-C_6H_{13}	O	135–137 (0.5)	43	1.5095[c]	$C_{10}H_{17}NO_2S$	14.86	14.72	[d]	
$CH_3O(CH_2)_2$	O	120–125 (1.5)	34	1.4872	$C_7H_{11}NO_3S$	[e]			
CH_3	S	82–83	81		$C_5H_7NOS_2$	[f]			
C_2H_5	S	66–67	70		$C_6H_9NOS_2$	[g]			
n-C_3H_7	S	127–128 (0.4)	55	1.6272	$C_7H_{11}NOS_2$	[f]			
n-C_4H_9	S	142–143 (0.5)	63	1.6080	$C_8H_{13}NOS_2$	[f]			
n-C_6H_{13}	S	170–172 (0.4)	55	1.5852	$C_{10}H_{17}NOS_2$	22.06	21.76	9.64	9.43
$CH_3O(CH_2)_2$	S	56.3–57.0	50		$C_7H_{11}NO_2S_2$	30.24	29.66	6.83	7.04
$HOOC(CH_2)_2O(CH_2)_2$	S	100–101	11		$C_9H_{13}NO_4S_2$	24.33	24.20	5.32	5.88
o-$CH_3OC_6H_4$	S	109.5–110	71		$C_{11}H_{11}NO_2S_2$	25.29	25.03	5.53	5.75
$CH_2{=}CH{-}CH_2$	S	145–147 (0.5)	64	1.6383[h]	$C_7H_9NOS_2$[i]	34.20	34.30	7.48	7.06

[a] All melting points corrected. [b] *Anal.* Calcd.: C, 45.28; H, 5.66. Found: C, 45.52; H, 5.52. [c] Refractive index at 28°. [d] *Anal.* Calcd.: C, 55.81; H, 7.91. Found: C, 55.87; H, 8.03. [e] *Anal.* Calcd.: C, 43.39; H, 5.82. Found: C, 43.83; H, 6.35. [f] J. L. Garraway, *J. Chem. Soc.*, 4072 (1962), reports CH_3, m.p. 82°; n-C_3H_7, b.p. 127–128° (0.4 mm.); n-C_4H_9, b.p. 142–143° (0.5 mm.). [g] T. L. Gresham, J. E. Jansen, and F. W. Shaver, *J. Am. Chem. Soc.*, **70**, 1001 (1948), report m.p. 66–67°. [h] Refractive index at 20°; yellow liquid. [i] *Anal.* Calcd.: C, 44.91; H, 4.81. Found: C, 45.05; H, 5.22.

alkyl resonance when the nitrogen is flanked by carbonyl and thiocarbonyl groups, since 3-allylrhodanine also showed the N-methylene resonance in this region.

The propionic acids prepared are listed in Tables I and II along with their physical constants. Table III describes the thiazane derivatives along with their physical properties.[8]

Biological Activities. (A).—Tests for the ability of some of these compounds to protect mice against X-irradiation have been carried out at the Walter Reed Army Institute of Research. None of the compounds showed activity in mice irradiated with 825 r. at the drug level range indicated. The results are summaried in Table IV.

TABLE IV

ANTIRADIATION PROPERTIES OF PROPIONIC ACIDS AND 1,3-THIAZANE DERIVATIVES IN MICE

Compound	Drug level, mg./kg.	Activity at 825 r.
β-Methylthiocarbamoylmercaptopropionic acid	350–370	None
β-*n*-Propylthiocarbamoylmercaptopropionic acid	150–350	None
β-*n*-Butylthiocarbamoylmercaptopropionic acid	350–370	None
β-Methylcarbamoylmercaptopropionic acid	150–350	None
β-Ethylcarbamoylmercaptopropionic acid	350–370	None
β-*n*-Butylcarbamoylmercaptopropionic acid	350–750	None
β-(2-Hydroxyethylthiocarbamoyl)-mercaptopropionic acid	350–370	None
1,3-Thiazane-2-thione-4-one[a]	350–750	None
3-Methyl-1,3-thiazane-2-thione-4-one	350–370	None
3-Ethyl-1,3-thiazane-2-thione-4-one	150–350	None
3-*n*-Propyl-1,3-thiazane-2-thione-4-one	150–350	None
3-(β-Methoxyethyl)-1,3-thiazane-2-thione-4-one	350–370	None
3-(5-Carboxy-3-oxapentyl)-1,3-thiazane-2-thione-4-one	150–350	None
1,3-Thiazane-2,4-dione	350–750	Slight (at 525 r.)
3-*n*-Propyl-1,3-thiazane-2,4-dione	150–350	None
3-*n*-Butyl-1,3-thiazane-2,4-dione	350–750	None
3-*n*-Hexyl-1,3-thiazane-2,4-dione	150–350	None

[a] T. L. Gresham, J. E. Jansen, and F. W. Shaver, *J. Am. Chem. Soc.*, **70**, 1001 (1948).

(B).—β-*n*-Butylthiocarbamoylmercaptopropionic acid, 3-methyl-1,3-thiazane-2-thione-4-one, and 3-*n*-butyl-1,3-thiazane-2-thione-4-one were tested for nematocidal activity, but were inactive in these tests.[9]

Experimental

General Procedure for the Preparation of β-Alkylthiocarbamoylmercaptopropionic Acids. (A) Sodium or Potassium Alkyldithiocarbamates.—A solution of potassium or sodium hydroxide (1 mole) and alkylamine (1 mole) in 250–300 ml. of ethanol was cooled to 0–5°, and carbon disulfide (1 mole) was added dropwise with stirring, care being taken that the temperature did not rise above 5°. After the complete addition of carbon disulfide, the mixture was stirred for 2–3 hr. and left overnight. Alcohol was removed under reduced pressure, the mixture cooled, and the solid filtered and washed with ether (100–150 ml.). These salts were then used for the reaction with β-propiolactone.

(B) Reaction of Alkyldithiocarbamate Salts with β-Propiolactone.—A salt of an alkyldithiocarbamic acid (0.5 mole) was dissolved in 200–250 ml. of water, cooled to 0°, and stirred throughout the reaction. To this mixture, β-propiolactone (0.5 mole) was added dropwise, care being taken that the temperature was always maintained below 5°. After the complete addition of β-propiolactone, the mixture was stirred for 0.5 hr. more and then neutralized with 18% hydrochloric acid and again stirred for 2 hr. more. The solid was filtered, washed with ice-cold water, and dried. It was then recrystallized from benzene. In case the propionic acid which remained was a low melting or semisolid mass, it was extracted with ether, washed with water, and the ether extract was dried over anhydrous sodium sulfate. Solvent was removed under reduced pressure and the residue solidified after cooling. It was then recrystallized from benzene. The compounds all exhibited characteristic infrared peaks for NH, CH, and carboxyl carbonyl absorption and a strong band at 6.5 to 6.7 μ characteristic of dithiocarbamate.[10] The products are reported in Table I along with their physical constants.

β-Alkylcarbamoylmercaptopropionic Acids.—These acids were prepared according to the procedure described under the preparation of β-alkylthiocarbamoylmercaptopropionic acids, using carbon oxysulfide instead of carbon disulfide. In these preparations, carbon oxysulfide gas was passed into the alkaline alcoholic solutions of amines, and the reaction mixture used directly for the reaction with β-propiolactone. The rest of the procedure was exactly the same. These propionic acids showed the characteristic infrared peaks for NH, CH, carboxyl carbonyl, amide carbonyl, and C–N stretches.[9]

General Procedure for the Preparation of 3-Alkyl-1,3-thiazane-2-thione-4-ones.—A modified procedure of Gresham, *et al.*,[a] was used. β-Alkylthiocarbamoylmercaptopropionic acid (15 g.) was dissolved in 50–60 ml. of acetic anhydride and two drops of concentrated sulfuric acid was added. The mixture was stirred for 2 hr. at 55–70° by which time the solution became clear. Solid impurities were filtered hot, and the cooled clear solution was poured into ice-cold water, stirred, and let stand overnight. If solid precipitated, it was filtered, washed with 20–25 ml. of water, dried, and recrystallized as yellow plates or needles from benzene. If oil was formed, it was extracted with ether; the ether extract was washed with water and dried over anhydrous sodium sulfate. Ether was removed *in vacuo* and the yellow oil distilled under reduced pressure. The products are listed in Table III. They all show a characteristic amide carbonyl peak at 5.85 to 5.90 μ.

β-N-*n*-Butyl-N-acetylcarbamoylmercaptopropionic Acid.—β-*n*-Butylcarbamoylmercaptopropionic acid (25.6 g.) was dissolved in 115 ml. of acetic anhydride and two drops of concentrated sulfuric acid was added. The mixture was stirred and heated at 70° for 2 hr. when the solution became clear. Excess acetic anhydride was removed under reduced pressure and the residue was poured into ice-cold water, stirred, and let stand overnight. The oil which separated was extracted with ether and the ether extract dried over anhydrous sodium sulfate. Ether was removed under reduced pressure and 13.7 g. of product distilled as colorless oil at 128–130° (0.5 mm.).

3-Ethyl-1,3-thiazane-2,4-dione.—β-Ethylcarbamoylmercaptopropionic acid (17.7 g.) was dissolved in 25 ml. of acetic anhydride and 2 drops of concentrated sulfuric acid was added. The mixture was refluxed for 8–10 hr., the excess of acetic anhydride removed under reduced pressure, and the product poured into ice-cold water, stirred, and let stand overnight. The oil which separated was extracted with ether and the ether extract was dried over anhydrous sodium sulfate. Ether was removed under pressure and 6.4 g. of product distilled at 118–120° (1 mm.) as a yellow oil (see Table III).

General Procedure for the Preparation of 3-Alkyl-1,3-thiazane-2,4-diones.—β-Alkylcarbamoylmercaptopropionic acid (0.1 mole) was placed in a 100-ml. round-bottomed flask fitted with a condenser carrying a calcium chloride guard tube. Thionyl chloride (0.2 mole) was added to the acid and the mixture was left at room temperature until the evolution of hydrogen chloride ceased. Then the reaction mixture was heated on a steam bath with occasional shaking for 1 hr. Excess thionyl chloride was removed

(8) After completion of this work, a paper by J. L. Garraway (*J. Chem. Soc.*, 4072 (1962)) appeared describing the synthesis of some compounds reported here.

(9) Personal communication from Dr. Dean Katsaros, of the Morton Chemical Co., Woodstock, Ill.

(10) T. L. Gresham, J. E. Jansen, and F. W. Shaver, *J. Am. Chem. Soc.*, **70**, 1001 (1948).

under reduced pressure and the product was poured into ice-cold water, extracted with ether, and the ether extract dried over anhydrous sodium sulfate. Solvent was removed, and the product was distilled if it was an oil. The solid thiazanediones were recrystallized from benzene. The compounds are listed in Table III. The thiazanediones all exhibited amide carbonyl and carbamoyl carbonyl peaks at 5.8 to 5.9 μ and at 6 to 6.15 μ, respectively.

3-(5-Carboxy-3-oxapentyl)-1,3-thiazane-2-thione-4-one.—The reaction mixture obtained by the reaction of sodium (2-hydroxyethyl)dithiocarbamate and β-propiolactone according to the general procedure described was added to 600 ml. of boiling 6 *N* hydrochloric acid. No solid was precipitated when the mixture was allowed to cool. Water was then removed under reduced pressure and a white solid product was obtained. It recrystallized from water in colorless plates in 11% yield. Analytical results proved this compound to be 3-(5-carboxy-3-oxapentyl)-1,3-thiazane-2-thione-4-one. The infrared spectrum showed the amide carbonyl band at 5.85 μ and carboxyl carbonyl peak at 6.1 μ.

Acknowledgment.—We thank Dr. Walter L. Meyer for his assistance in interpreting the n.m.r. spectra, Dr. Dean Katsaros of Morton Chemical Co., Woodstock, Ill., for testing the compounds for the nematocidal activity, and Dr. D. P. Jacobus and staff, of the Walter Reed Army Institute of Research, for the information on antiradiation tests.

The Synthesis and Preliminary Pharmacology of Some 9*H*-Pyrido[3,4-*b*]indoles (β-Carbolines)[1] and Tryptamines Related to Serotonin and Melatonin[2]

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A series of β-carbolines and tryptamines related to serotonin and melatonin has been synthesized. These included a number of tetrahydro-β-carbolines with substituents in the 1, 2, or 6 positions. An unusual oxidative transformation of one of the compounds, 2-acetyl-6-hydroxy-1-methyl-1,2,3,4-tetrahydro-β-carboline, was observed. Preliminary pharmacological investigations of these new compounds consisted of examining their ability to antagonize the myotropic action of serotonin and to effect a conditioned behavioral reflex in rats. Most of the compounds showed some activity in both experimental preparations, with several exhibiting high potency in both. Since use can be made of these materials in the characterization of metabolites of serotonin and melatonin, their chromatographic and spectral properties are reported.

Many known psychotomimetic compounds such as lysergic acid derivatives, psilocybin, and harmaline are substituted indoles or carbolines. The psychotomimetic action of lysergic acid diethylamide was originally postulated as being due to its ability to antagonize the action of serotonin.[3] It had been demonstrated further that although melatonin had no effect on avoidance escape behavior, cyclodehydration to 1-methyl-6-methoxy-3,4-dihydro-β-carboline yielded a compound which proved to be a potent serotonin antagonist and to exert a profound effect on conditioned behavior.[4] The idea that such compounds might arise endogenously has been entertained as a possible biochemical explanation for psychosis.[5] Recently, evidence has been put forth for the presence of a compound in pineal tissue which does not give a typical Ehrlich indole reaction and is a serotonin antagonist. On this tenuous basis it has been suggested that a carboline could be present in pineal tissue.[6] The isolation and characterization of melatonin, an indole derivative, from pineal tissue[7] provides further impetus to look for indolic substances in this gland for which so many functions have been postulated.[8-10] The minute amounts of physiologically active compounds present have made classical means of identification impractical. Thus, it was important to these investigations to embark on a program of synthetic chemistry to provide a variety of classes of authentic indolic compounds for comparative purposes. In general the compounds prepared were of types that could arise conceivably from the metabolism of serotonin or melatonin. Because of the close relationship of these compounds to known psychotomimetic indoles, they have provided a valuable series for our pharmacological studies.

Structural class representatives have been prepared rather than attempting to synthesize many isomers of one structure so that a profile of general characteristics for different types of compounds would be available. The Pictet–Spengler reaction (Fig. 1) has been established as a general and reliable method for the conversion of tryptamines to 1,2,3,4-tetrahydro-β-carbolines,[11]

(1) The β-carboline nomenclature is cited in "The Ring Index" as preferred nomenclature, while the pyridoindole nomenclature is used in the *Chemical Abstracts* indexes. The pyridoindole nomenclature does possess greater potential for describing all of the various, theoretically possible isomers of these heterocyclic systems. However, some ambiguity can arise in the use of that nomenclature. Thus, the *Chemical Abstracts* index [*Chem. Abstr.*, **57**, 516*s* (1962)] equates β-carboline to 9*H*-pyrido[3,4-*b*]indole. According to the established pyridoindole nomenclature rules, then harmine, 1-methyl-6-methoxy-β-carboline, becomes 7-methoxy-1-methyl-9*H*-pyrido[3,4-*b*]indole whereas harmaline, 1-methyl-6-methoxy-1,2-dihydro-β-carboline, is described as 4,9-dihydro-7-methoxy-1-methyl-3*H*-pyrido[3,4-*b*]indole. That this can sometimes give rise to two sets of pyridoindole nomenclature for the same compound is illustrated by the fact that a chemical compendium as the "Merck Index" uses the name 3,4-dihydro-7-methoxy-1-methyl-9*H*-pyrido[3,4-*b*]indole for harmaline. Since this paper is concerned only with the one isomer of these heterocycles, use has been made of the preferred nomenclature of "The Ring Index" calling the series β-carbolines.

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