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.

(2) The authors wish to thank Mrs. Gertrude H. Britton for her generous financial support.

(3) D. W. Woolley and E. Shaw, *Science*, **119**, 587 (1954).

(4) W. M. McIsaac, P. A. Khairallah, and I. H. Page, *ibid.*, **134**, 674 (1961).

(5) W. M. McIsaac, *Postgrad. Med.*, **30**, 111 (1961).

(6) G. Farrell, and W. M. McIsaac, *Arch. Biochem. Biophys.*, **94**, 543 (1961).

(7) A. B. Lerner, J. D. Case, and Y. Takashi, *J. Biol. Chem.*, **235**, 1922 (1960).

(8) J. I. Kitay and M. D. Altschule, "The Pineal Gland," The Harvard University Press, Cambridge, Mass., 1954.

(9) G. Farrell, *Recent Progr. Hormone Res.*, **15**, 275 (1959).

(10) L. Baschieri, F. DeLuca, L. Cramarossa, C. DeMartino, A. Oliverio, and M. Negri, *Experientia*, **19**, 15 (1963).

(11) W. M. Whaley and T. R. Govindarchari, "Organic Reactions," Coll. Vol. 6, John Wiley and Sons, Inc., New York, N. Y., 1951, pp. 151–190.

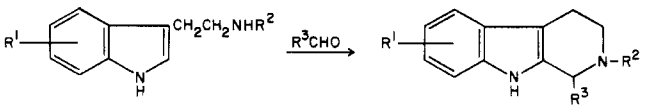

Fig. 1.—A generalized scheme of the Pictet–Spengler reaction.

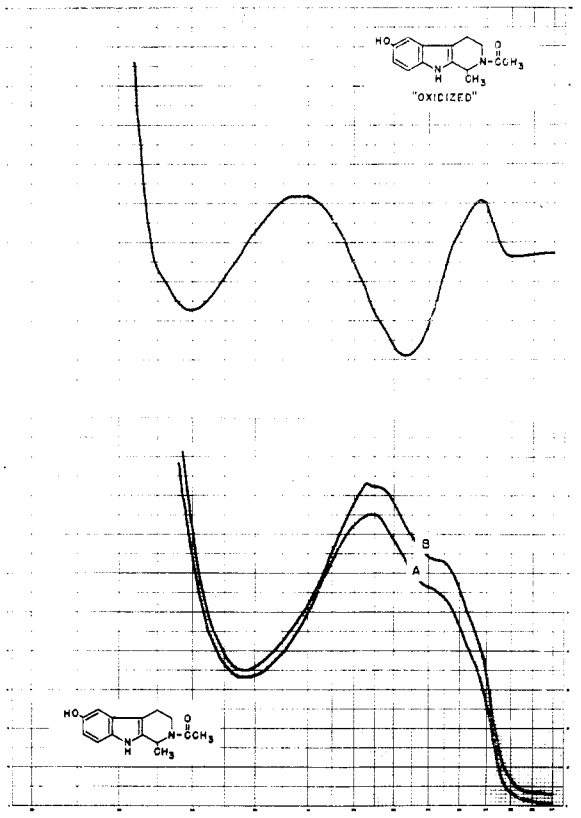

Fig. 2.—Ultraviolet absorption spectra of a sample of 2-acetyl-6-hydroxy-1-methyl-1,2,3,4-tetrahydro-β-carboline: A, immediately after synthesis; the upper curve, upon standing in air for several weeks; B, the oxidized form after treatment with palladium and ethanol.

and extensive use has been made of it in the present study. It was desirable to prepare a carboline that could result directly from serotonin. Acetaldehyde was chosen as the other reactant because of its physiological significance and because it reacts generally more successfully in the Pictet–Spengler reaction with tryptamines than most other aldehydes.

In initial experiments a variety of conditions were explored with the stable and physiological form of serotonin, the creatinine sulfate, to elucidate its reaction with acetaldehyde. However, only inseparable mixtures which seemingly contained the desired product were obtained. In light of these results, it was decided to approach the synthesis through 5-benzyloxytryptamine and again a variety of conditions were explored. In initial reactions where a low yield (28%) of the desired di(6-benzyloxy-1-methyl-1,2,3,4-tetrahydro-β-carboline) sulfate monohydrate had been obtained, the product had been accompanied by a large amount of red, resinous, high-melting solid. Subsequently it was shown that pH was a critical factor and that a good yield of pure 6-benzyloxy-1-methyl-1,2,3,4-tetrahydro-β-carboline hydrochloride could be obtained when the reaction was carried out at pH 6. With this pure intermediate all subsequent conversions led to very pure products in contrast to earlier attempts with materials obtained at pH 2.

Thus, the hydrochloride in aqueous solution was converted to the free base with sodium carbonate, which was then readily acetylated with pyridine and acetic anhydride to yield 2-acetyl-6-benzyloxy-1-methyl-1,2,3,4-tetrahydro-β-carboline. The acetylated material was then debenzylated with hydrogen over 10% palladium-on-charcoal to yield 2-acetyl-6-hydroxy-1-methyl-1,2,3,4-tetrahydro-β-carboline. 6-Benzyloxy-1-methyl-1,2,3,4-tetrahydro-β-carboline hydrochloride was debenzylated with hydrogen in the same manner to give 6-hydroxy-1-methyl-1,2,3,4-tetrahydro-β-carboline hydrochloride, the carboline directly related to serotonin. It was an off-white solid stable in air for several weeks as indicated by ultraviolet spectra.

In several preliminary studies a less pure sample of the 2-acetyl-6-hydroxy-1-methyl-1,2,3,4-tetrahydro-β-carboline had been obtained. That material upon standing for several weeks in air underwent a modification in its ultraviolet spectrum as shown in Fig. 2, indicating a transformation to another compound. However, it was then possible to re-establish the original spectrum by treating the "oxidized" material with palladium in refluxing ethanol. Ordinarily, this system had been shown to convert tetrahydrocarbolines to the fully aromatic analogs[12]; however, in the above instance the system acted in an opposite manner. Furthermore, the acetyl group prevented that type of compound from being converted to the fully aromatic carboline. Examination of the ultraviolet spectra of a tetrahydrocarboline, a dihydrocarboline, and a fully aromatic carboline, as shown in Fig. 3, shows an increase in the wave length where the compounds absorb, characteristic for each compound class. However, upon comparing the spectra for the oxidatively transformed 2-acetyl-6-hydroxy-1-methyl-1,2,3,4-tetrahydro-β-carboline with those above, it can be seen that a different type of conversion is taking place. Furthermore, chromatography shows R_f 0.85 in solvent 3 (Table I) for the original compound against 0.55 for the oxidized material. More significantly, the starting carboline gives a positive Gibb's reaction (2,6-dichloroquinone chloroimide) for the hydroxyl group, whereas the oxidized form no longer does. Treatment of the oxidized material with palladium in ethanol restores the original R_f, positive Gibb's reaction, and ultraviolet spectra.

It appears that the 6-hydroxy group either underwent an oxidation to a probable quinoneimine or else a keto–enol tautomeric shift to a keto form under the catalytic influence of oxygen (Fig. 4). If the latter occurred, then palladium served as an enolization catalyst. The observation of keto–enol tautomerism of aromatic hydroxy compounds has been observed in many instances.[13] On the other hand, the ease of oxidation of hydroxyindoles to quinones has also been established, particularly in studies attempting to describe the formation and structure of melanin.[14] Isolation and characterization of the oxidized form to de-

(12) C. F. Huebner, H. A. Troxell, and C. Schroeder, *J. Am. Chem. Soc.*, **75**, 5887 (1953).

(13) G. W. Wheland, "Advanced Organic Chemistry," 3rd Ed., John Wiley and Sons, Inc., New York, N. Y., 1960, Chap. 14.

(14) J. D. Bu'lock and J. Harley-Mason, *J. Chem. Soc.*, 703 (1951).

cide whether oxidation or tautomerism occurred was not included in this study.

Di(8-benzyloxy-1-methyl-1,2,3,4-tetrahydro-β-carboline) sulfate was prepared in 78% yield and was a stable compound; however, on debenzylation the resultant hydroxycarboline proved to be unstable. Its solutions when exposed to air formed a purple product of low solubility which on further standing was converted to an even less soluble brown substance.

An attempt was made to synthesize 1,2-dimethyl-6-methoxy-1,2,3,4-tetrahydro-β-carboline by condensing 5-methoxy-N-methyltryptamine with acetaldehyde. This was done in two steps, first using a mild reaction to form a Schiff's base, then further treating the Schiff's base at pH 2. Chromatography indicated that a mixture of products had formed, the major constituent being the desired carboline which was then isolated and identified as a picrate. The reaction was repeated at several conditions and at pH 6, but no improvement in the quality of the product could be achieved.

α-Ketoglutaric acid is a carbonyl compound of interest because of its role in pyruvate metabolism and transamination in the brain.[15] Tryptamine has been shown to form a carboline when condensed with α-ketoglutaric acid.[16] This reaction was repeated using 5-methoxytryptamine, a molecule more closely related to serotonin. The reaction went successfully first to 1-carboxy-1-(2-carboxyethyl)-6-methoxy-1,2,3,4-tetrahydro-β-carboline (I). It was then possible to cyclize this intermediate further by means of hydrogen chloride catalysis to the hitherto unreported lactam, 10-methoxy-6-oxo-2,3,4,5,6-pentahydro-*1H*-indolo[3,2,1-*de*][1,5]-naphthyridine (II, Fig. 5). The relative ease of this intramolecular acylation of the indole nitrogen is significant in comparison to the much greater difficulty with intermolecular acylations. This reaction provides another example of what might be considered a model enzyme system where the entropy factor due to molecular motions is reduced, providing the reaction with the benefits of a greater negative free energy change.

Pyridoxal, another physiological aldehyde, condensed with 5-methoxytryptamine to form 1-(3-hydroxy-5-hydroxymethyl-2-methyl-4-pyridyl)-6-methoxy-1,2,3,4-tetrahydro-β-carboline, which also should be of interest to the area of pyridoxine biochemistry.

Direct N-methylation of 6-methoxy-1-methyl-1,2,3,4-tetrahydro-β-carboline with methyl iodide yielded the N-methyl quaternary ammonium iodide, a stable white salt. Acetylation of the same carboline with acetic anhydride in pyridine proceeded readily to give 2-acetyl-6-methoxy-1-methyl-1,2,3,4-tetrahydro-β-carboline related to melatonin. In a similar manner, 2-acetyl-1-methyl-1,2,3,4-tetrahydro-β-carboline was also prepared. 6-Methoxy-1-methyl-1,2,3,4-tetrahydro-β-carboline, when treated with butyric anhydride and pyridine, yielded the N-butyryl derivative, a longer chained fatty acid amide.

Although there is no reported instance of simple ketones reacting in the Pictet–Spengler reaction, the possibility was investigated. Thus, serotonin creatinine sulfate and acetone were incubated at 37° for 3 days. Isolation of the product yielded 81% of unchanged starting material, identified and shown to be homogeneous by its color reactions and migration on a silica thin layer on glass.

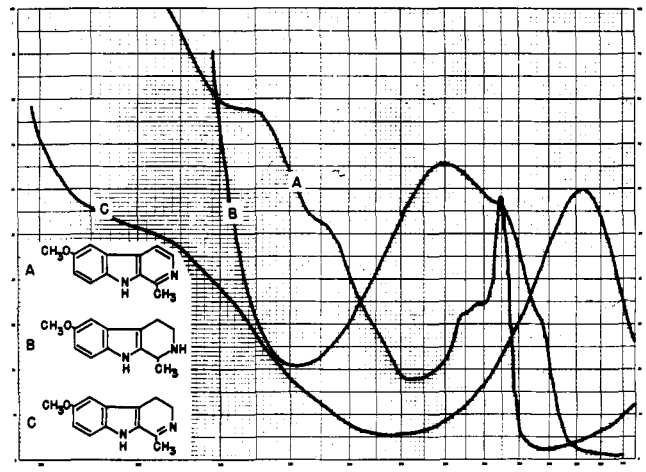

Fig. 3.—Ultraviolet absorption spectra of three carbolines differing only in their degree of saturation of the C-ring. Curve A is of 6-methoxy-1-methyl-β-carboline, curve B is of 6-methoxy-1-methyl-1,2,3,4-tetrahydro-β-carboline, and curve C is of 1,2-dihydro-6-methoxy-1-methyl-β-carboline.

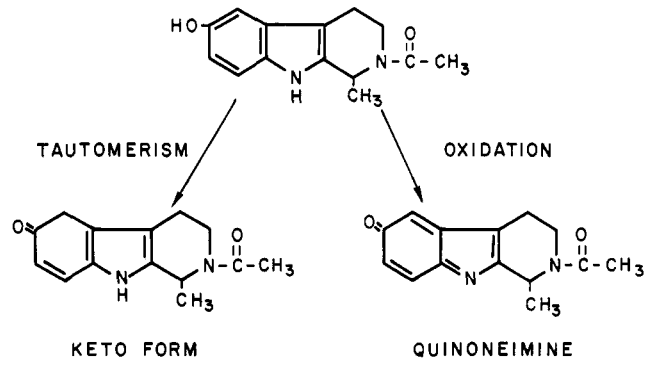

Fig. 4.—Two possible modes by which 2-acetyl-6-hydroxy-1-methyl-1,2,3,4-tetrahydro-β-carboline could be effected by oxygen.

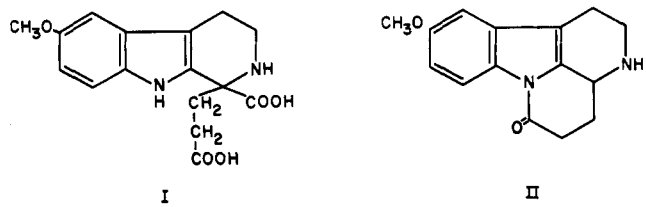

Fig. 5.—Structures of 1-carboxy-1-(2-carboxyethyl)-6-methoxy-1,2,3,4-tetrahydro-β-carboline (I) and 10-methoxy-6-oxo-2,3,4,5,6-pentahydro-*1H*-indolo[3,2,1-*de*][1,5]naphthyridine (II).

Carbolines containing a 3,4-dimethoxybenzyl group in the 1-position were prepared. Such materials resulted from condensation between tryptamine or 5-methoxytryptamine and 3,4-dimethoxyphenylacetaldehyde. The latter aldehyde could occur physiologically, since evidence exists that its hypothetical precursor, the corresponding amine, may be a physiological substance.[17]

Both tryptamine and 5-methoxytryptamine readily underwent a Pictet–Spengler condensation with 3,4-

(15) H. McIlwain, "Biochemistry and the Central Nervous System," 2nd Ed., Little, Brown and Co., Boston, Mass., 1959.

(16) G. Hahn, *Ber.*, **71**, 2163 (1938).

(17) A. J. Friedhoff and E. Van Winkle, *J. Nervous Mental Disease*, **6**, 550 (1962).

TABLE I

CHARACTERISTICS OF SOME COMPOUNDS RELATED TO SEROTONIN

Compound	Color reactions[a]			R_f values[b]			Fluorescent spectra[c]		Ultraviolet spectra[d]	Serotonin antagonism	Effect on V.I. behavior[e]				
	Xanthydrol	Ehrlich	Gibbs	1	2	3	λ_a, mμ	λ_e, mμ	λ_{max}, mμ		Dose, μmoles/kg.	1	2	3	4
3-(2-Aminoethyl)-5-methoxyindole				0.00	0.76	0.50	390	475	257, 302	−	10	−7.6	−9	0	−22
1-Benzyl-1,2,3,4-tetrahydro-β-carboline hydrochloride	Magenta			0.62	0.90	0.82	260, 300	350	272, 279, 289	++	20	+22	+5.8	+28	+41
2-Carboxy-5-methoxyindole	Blue	Blue		0.30	0.36	0.83	275, 350	420	294						
1-Carboxy-1-(2-carboxyethylmethoxy-1,2,3,4-tetrahydro-β-carboline		Gray		0.01	0.13	0.54	300	350	283	+					
10-Methoxy-6-oxo-2,3,4,5,6-pentahydro-1*H*-indolo [3,2,1-*de*]-[1,5] naphthyridine	Magenta			0.30	0.80	0.65	350	410	253, 298, 308	++++	16	−3	−40	−44	−27
1-(3-Hydroxy-5-hydroxymethyl-6-methoxy-2-methyl-4-pyridyl)-1,2,3,4-tetrahydro-β-carboline	Blue			0.25	0.80	0.62	310	375	292 (sh. 275)[f]	++					
1,2-Dimethyl-6-methoxy-1,2,3,4-tetrahydro-β-carboline	Blue	Gray		0.25	0.90	0.70	265, 330	260		−					
5-Methoxyisatin	Orange	Orange		0.85	0.75	0.82	300	350	253 (sh. 262)	−					
2-Acetyl-6-hydroxy-1-methyl-1,2,3,4-tetrahydro-β-carboline	Blue	Blue	Blue	0.65	0.84	0.85	300	350	enol 275 (sh. 295) keto 258, 308	++	16	−24	+30	−18	−3.2
6-Hydroxy-1-methyl-1,2,3,4-tetrahydro-β-carboline hydrochloride	Blue	Blue	Blue	0.00	0.75	0.57	260	360	276 (sh. 298, 308)	+++	16	+34	−6	−3.5	−26
2-Acetyl-6-methoxy-1-methyl-1,2,3,4-tetrahydro-β-carboline	Blue	Blue		0.85	0.87	0.90	310	350	275 (sh. 295, 303)	±	18	−8	−9	0	−51
N-Methyl-5-methoxytryptamine hydrochloride	Blue	Blue		0.07	0.86	0.65	330	350	275 (sh. 293)[f]	Oxytocic	27	−50	−64	−84	−91
6-Methoxy-1,2,2-trimethyl-1,2,3,4-tetrahydro-β-carboline iodide	Gray			0.05	0.55	0.64	265, 320	350	272 (sh. 292, 304)[f]	−	8	+18	+14	+6	−19
2-Acetyl-1-methyl-1,2,3,4-tetrahydro-β-carboline	Blue			0.80	0.90	0.92	300	350	226, 278 (sh. 295, 309)	−					
2-Butyryl-1-methyl-1,2,3,4-tetrahydro-β-carboline	Blue			0.85					276 (sh. 295, 308)	−					
1-(3,4-Dimethoxybenzyl)-1,2,3,4-tetrahydro-β-carboline	Magenta			0.58	0.92	0.82	310	340	279	++++	12	−10	−50	−40	0
1-(3,4-Dimethoxybenzyl)-6-methoxy-1,2,3,4-tetrahydro-β-carboline	Blue			0.60	0.86	0.78	325	340	225 (sh. 309)	+++−	12	−5	−9	−13	−12

[a] Reagents used were: xanthydrol, 2% in ethanol plus a few drops of concn. HCl; Ehrlich (dimethylaminobenzaldehyde) in 1.5 *N* HCl; Gibbs 2%, 2,6-dichloroquinonechloroimide in ethanol followed by saturated sodium bicarbonate. [b] Solvents used were: 1, chloroform–methanol (9:1, silica gel thin layer chromatography); 2, 1-propanol–ammonia (8:2); 3, 1-butanol–acetic acid–water (4:1:5). [c] In ethanol at pH 7. [d] In ethanol at pH 7; sh. denotes a shoulder. [e] Percentile change during each quarter of experimental session related to means based on five control periods (see Experimental). [f] In water at pH 1.

dimethoxyphenylacetaldehyde[18] in aqueous alcohol at room temperature at pH 4–6, after several days standing, to yield the corresponding tetrahydrocarboline hydrochlorides. 1-(3,4-Dimethoxybenzyl)-1,2,3,4-tetrahydrocarboline had been prepared previously, however, by using 3,4-dimethoxyphenylpyruvic acid and subsequently decarboxylating the 1-carboxy intermediate.[19]

It was found that great variations of optimum conditions of the Pictet–Spengler reactions are required by each pair of reactants. This "perplexing variation of yields under different conditions for several reactants" has been previously commented upon in a review.[20]

5-Methoxy-*N*-methyltryptamine was prepared following the method of Wilkinson, beginning with 5-methoxytryptamine, carrying out a tosylation, methylation, and detosylation on that material.[21] However, by a modification of the reported isolation procedure it was possible to prepare the free base, previously unreported, in good purity and yields.

A second tryptamine prepared was related to serotonin through O-methylation and oxidation in the 2-position, *i.e.*, the oxindole. That compound was synthesized by starting with *p*-anisidine and in five steps preparing the 5-methoxy-3-oxindolylacetonitrile.[22] By means of a limited careful hydrogenation over a platinum oxide catalyst it was possible to reduce preferentially the nitrile group to the amino function, leaving the carbonyl group intact to give 2,3-dihydro-5-

(18) E. Kaufman, E. Eliel, and J. Rosenkranz, *Ciencia* (Mex.), **7**, 136 (1946).
(19) Ref. 11, p. 174.
(20) Ref. 11, p. 172.
(21) S. Wilkinson, *J. Chem. Soc.*, 2079 (1958).
(22) S. Pietra, *Farmaco* (Pavia), *Ed. Sci.*, **13**, 75 (1958).

methoxy-2-oxotryptamine in reasonable yield, readily purified by crystallization.

Pharmacological Activity.—Many of the compounds in this series were found to be potent antagonists of the myotropic action of serotonin in the isolated rat uterus assay, and significant changes in potency resulted from minor modifications in chemical structure as shown in Table I.

A large number of compounds prepared in this study exhibited significant effect on conditioned behavioral response rates of rats (Table I). Considerable variation of this effect was seen with each structural change varying from materials that had no activity to those of a high order of potency. For this reason, and since they all bear some structural relationship to known psychotomimetic substances, a more detailed study is in progress to elucidate the structure–activity relationship of these compounds.

Since some of the compounds may be the same as, or related to, active agents in pineal tissue, their effects are being studied on other physiological functions in which this gland has been implicated.

Experimental[23]

Reactions between Serotonin Creatinine Sulfate and Acetaldehyde.—In an attempt to prepare 6-hydroxy-1-methyl-1,2,3,4-tetrahydro-β-carboline directly by means of the Pictet–Spengler reaction, serotonin creatinine sulfate and acetaldehyde were allowed to react under a variety of conditions of time, pH, temperature, and ratios of reactants. Products were obtained that gave a positive reaction for the hydroxyl group (Gibb's) and for the indole (xanthydrol) but were negative for the indole 2-position (Ehrlich), indicating hydroxytetrahydrocarboline formation. In addition, the products in bioassays were potent serotonin antagonists and caused aldosterone secretion in decerebrate animals, properties characteristic of carbolines.[6] However, the products were sometimes high melting (above 300°) and even upon repeated crystallization had elemental analyses that were at times near to those required but were never acceptable matches. Furthermore, a variety of different melting materials were obtained suggesting that these attempts yielded mixtures of products.

6-Benzyloxy-1-methyl-1,2,3,4-tetrahydro-β-carboline Sulfate.—5-Benzyloxytryptamine sulfate (300 mg., 8.25×10^{-4} mole), 6.0 ml. of 10% acetaldehyde, 6.0 ml. of water, and 1.0 ml. of 2 *N* sulfuric acid were heated at 90° for 20 min. At the end of this time an orange precipitate began to appear, and the reaction mixture was immersed in ice to furnish 282 mg. of an orange product. The material was crystallized from 30.0 ml. of water containing several milliliters of 2 *N* sulfuric acid to yield 80 mg. (28%) of 6-benzyloxy-1-methyl-1,2,3,4-tetrahydro-β-carboline sulfate monohydrate, m.p. 250–252° dec.

Anal. Calcd. for $C_{38}H_{42}N_4O_7S$: C, 65.49; H, 6.08; N, 8.05; S, 4.60. Found: C, 65.20; H, 6.18; N, 7.90; S, 5.01.

A number of variations in time, reaction temperature, and amounts of reagent were carried out in attempts to improve the yield; however, in each case a low yield resulted with either an orange gummy product, or an orange powder containing a large amount of soluble, high melting impurity (probably polymer). However, in a first experiment where the pH of the reaction was varied from 2–6, the yield and quality of the product markedly improved, and those conditions, using 5-benzyloxytryptamine hydrochloride, are described below.

6-Benzyloxy-1-methyl-1,2,3,4-tetrahydro-β-carboline Hydrochloride.—5-Benzyloxytryptamine hydrochloride (250 mg., 8.3×10^{-4} mole), 6.0 ml. of 10% acetaldehyde, and 6.0 ml. of water were incubated (pH 6) for 1 hr. at 85°. While cold, the amine salt did not dissolve; however, upon heating the mixture, a clear solution was obtained. It was cooled in ice and filtered to give 254 mg. (93% yield) of white crystals, m.p. 235–237°. A small portion was crystallized from water for an analytical sample.

Anal. Calcd. for $C_{19}H_{21}ClN_2O$: C, 68.67; H, 6.44; Cl, 10.78; N, 8.52. Found: C, 68.91; H, 6.48; Cl, 10.45; N, 8.71.

The base, 6-benzyloxy-1-methyl-1,2,3,4-tetrahydro-β-carboline, was prepared by the addition of 10% sodium carbonate solution to a saturated solution of the hydrochloride to pH 9 and then extracting with chloroform. Reduction of the volume of the combined chloroform extracts with the addition of a large excess of heptane produced a copious precipitate which on filtering and drying melted at 160–163°.

Anal. Calcd. for $C_{19}H_{20}N_2O$: C, 76.27; H, 6.90; N, 9.58. Found: C, 76.46; H, 7.05; N, 9.43.

2-Acetyl-6-benzyloxy-1-methyl-1,2,3,4-tetrahydro-β-carboline.—6-Benzyloxy-1-methyl-1,2,3,4-tetrahydro-β-carboline (140 mg., 4.8×10^{-4} mole) was dissolved in 1.0 ml. of pyridine and 0.3 ml. of acetic anhydride resulting in warming and a deepening of color. After 24 hr. at room temperature the reaction mixture was poured into 10 ml. of benzene to which 35.0 ml. of heptane was then added. A heavy precipitate of the product formed, and the mixture was cooled at 5° for 2 hr.; filtration yielded 121 mg. (76%) of product, m.p. 200–202°.

Anal. Calcd. for $C_{21}H_{22}N_2O_2$: C, 75.44; H, 6.63; N, 8.38. Found: C, 75.42; H, 6.46; N, 8.53.

2-Acetyl-6-hydroxy-1-methyl-1,2,3,4-tetrahydro-β-carboline.—2-Acetyl-6-benzyloxy-1-methyl-1,2,3,4-tetrahydro-β-carboline (120 mg., 3.6×10^{-4} mole) was dissolved in 20 ml. of ethyl acetate and debenzylated in a Parr low pressure hydrogenator under 2.8 kg./cm.^{2} of hydrogen for 18 hr. at room temperature with 50 mg. of 10% palladium-on-charcoal catalyst. The mixture was filtered through Celite and reduced in volume on a Rinco evaporator to 5.0 ml. Heptane (35 ml.) was added to precipitate the product. The mixture was cooled 4 hr. at 5°, filtered, and upon drying yielded 61.0 mg. (70%) of material, m.p. 221–224°.

Anal. Calcd. for $C_{14}H_{16}N_2O_2$: C, 68.83; H, 6.60; N, 11.47. Found: C, 68.56; H, 6.66; N, 10.59.

6-Hydroxy-1-methyl-1,2,3,4-tetrahydro-β-carboline Hydrochloride.— 6-Benzyloxy-1-methyl-1,2,3,4-tetrahydro-β-carboline hydrochloride (200 mg., 6.1×10^{-4} mole) was dissolved in 20.0 ml. of methanol, 40 mg. of 10% palladium–charcoal was added, and the mixture was hydrogenated in a Parr low pressure apparatus for 18 hr. at room temperature at 2.8 kg./cm.^{2} of hydrogen. The reaction solution was filtered through Celite, and the filtrate was evaporated to a gum on a Rinco evaporator. Acetone was added to the gum to furnish 122 mg. (84% yield) of a light gray substance, m.p. 266° dec.

Anal. Calcd. for $C_{12}H_{13}ClN_2O$: C, 60.37; H, 6.33; Cl, 14.85; N, 11.84. Found: C, 59.81; H, 6.52; Cl, 14.23; N, 11.78.

8-Benzyloxy-1-methyl-1,2,3,4-tetrahydro-β-carboline.—7-Benzyloxytryptamine (250 mg., 9.4×10^{-4} mole) was suspended in 12.0 ml. of 5% acetaldehyde. The mixture, with occasional shaking, was allowed to stand for 30 min., then 1.0 ml. of 2 *N* sulfuric acid was added, and the mixture was heated at 85–90° for 25 min. It was cooled at 5° overnight to yield a tan precipitate which on washing with acetone and drying amounted to 247 mg. (78%) of the sulfate salt, m.p. 210–212°. A portion was crystallized from dilute sulfuric acid to give an analytical sample.

Anal. Calcd. for $C_{38}H_{40}N_4O_6S$: C, 67.03; H, 5.92; N, 8.23; S, 4.71. Found: C, 66.76; H, 6.18; N, 8.31; S, 4.53.

1,2-Dimethyl-6-methoxy-1,2,3,4-tetrahydro-β-carboline.—5-Methoxy-N-methyltryptamine (250 mg., 1.2×10^{-3} mole) was dissolved in 6.0 ml. of water containing 0.5 ml. of 2 *N* sulfuric acid. The solution was filtered and neutralized to pH 6 with sodium carbonate. Six milliliters of 10% acetaldehyde was added, and the mixture was heated at 70° for 1 hr. Then 1.0 ml. of 2 *N* sulfuric acid was added, and the mixture was heated at 90° for 30 min. It was cooled and 10% sodium carbonate was added to adjust the solution to pH 8; the resulting precipitate was filtered. Additional precipitate was obtained upon adding 10% sodium carbonate to the filtrate getting a total of 188 mg. of product having a wide melting range starting at 110°. This material could not be purified by crystallization. However, confirmation that it was the crude carboline was obtained by preparing a picrate which was then crystallized from ethanol, m.p. 213–215° dec.

Anal. Calcd. for $C_{20}H_{21}N_5O_8$: C, 52.26; H, 4.61; N, 15.25. Found: C, 52.20; H, 4.68; N, 14.93.

Cyclization of 5-Methoxytryptamine with α-Ketoglutaric Acid.—α-Ketoglutaric acid (800 mg., 5.5×10^{-3} mole) and 700 mg. (3.6×10^{-3} mole) of 5-methoxytryptamine, dissolved in 15 ml. of ethanol, were stirred at room temperature overnight. A white

(23) All melting points are corrected. Microanalyses were performed by Micro-Tech Laboratories, Skokie, Ill.

precipitate began to appear after approximately 1 hr. The product was then filtered directly from the solution and dried under vacuum to yield 1.0 g. (100%) of 1-carboxy-1-(2-carboxyethyl)-6-methoxy-1,2,3,4-tetrahydro-β-carboline, m.p. 183–185°.

Anal. Calcd. for $C_{16}H_{18}N_2O_5$: C, 60.37; H, 5.69; N, 8.80. Found: C, 60.22; H, 5.57; N, 8.89.

It was dissolved in 25.0 ml. of methanolic hydrogen chloride, and the solution was refluxed overnight during which time a white solid settled out of the solution. The mixture was cooled and filtered to give 0.7 g. (76% yield) of 10-methoxy-6-oxo-2,3,4,5,6-pentahydro-*IH*-indolo[3,2,1-*de*][1,5]naphthyridine hydrochloride, m.p. 301–302°. Its identity was confirmed by converting the salt in hot water to the free base with sodium carbonate, the cream-colored product had m.p. 167–170°.

Anal. Calcd. for $C_{15}H_{17}N_2O_2$: C, 70.01; H, 6.66; N, 10.89. Found: C, 69.73; H, 6.19; N, 11.11.

Reaction of 5-Methoxytryptamine with Pyridoxal.—5-Methoxytryptamine (250 mg., 13.2×10^{-3} mole) was ground and dissolved in 6.0 ml. of water and 1.0 ml. of 2 *N* sulfuric acid. A solution of 250 mg. (13.2×10^{-3} mole) of pyridoxal hydrochloride in 6.0 ml. of water was added to a deepening yellow color, and the solution was incubated for 20 hr. at 37° and neutralized to pH 9 with 10% sodium carbonate. A yield of 316 mg. (71%) of 1-(3-hydroxy-5-hydroxymethyl-2-methyl-4-pyridyl)-6-methoxy-1,2,3,4-tetrahydro-β-carboline, m.p. 245° dec., was obtained. A portion was crystallized from ethanol–dimethylformamide and water for analysis.

Anal. Calcd. for $C_{19}H_{21}N_3O_3$: C, 67.24; H, 6.24; N, 12.38. Found: C, 66.65; H, 6.37; N, 11.89.

Reaction of Methyl Iodide with 6-Methoxy-1-methyl-1,2,3,4-tetrahydro-β-carboline.—6-Methoxy-1-methyl-1,2,3,4-tetrahydro-β-carboline (250 mg., 1.2×10^{-3} mole) was suspended in 0.5 ml. of ethanol and 0.2 ml. of 30% sodium hydroxide solution. Methyl iodide (0.2 ml., 460 mg., 3.2×10^{-3} mole) was added to the suspension which turned to a yellow solution, resolidifying upon cooling under a tap. The mixture was allowed to stand overnight and was filtered to give a quantitative yield (475 mg.) of 6-methoxy-1,2,2-trimethyl-1,2,3,4-tetrahydro-β-carboline 2-iodide, m.p. 228–232°. A portion was crystallized from ethanol and showed the presence of the iodide ion by the formation of free iodine upon adding chlorine water to a solution of the compound.

Anal. Calcd. for $C_{15}H_{21}IN_2O$: C, 48.39; H, 5.69; N, 7.53. Found: C, 48.38; H, 5.61; N, 7.03.

2-Acetyl-6-methoxy-1-methyl-1,2,3,4-tetrahydro-β-carboline.—6-Methoxy-1-methyl-1,2,3,4-tetrahydro-β-carboline (100 mg., 4.6×10^{-4} mole) was added to 0.2 ml. of acetic anhydride. Solution occurred immediately with warming, followed by copious precipitation after 1 min. The mixture was heated in boiling water for an additional 2 min. Several milliliters of water was added to the mixture, and the precipitate that formed was filtered, washed, and dried to yield 116 mg. (98%) of material, m.p. 203–204.5°.

Anal. Calcd. for $C_{15}H_{18}N_2O_2$: C, 69.74; H, 7.01; N, 10.85. Found: C, 69.21; H, 6.91; N, 10.85.

2-Acetyl-1-methyl-1,2,3,4-tetrahydro-β-carboline.—This material was prepared in 94% yield in the same manner as the preceding N-acetylated carboline, however, starting with 1-methyl-1,2,3,4-tetrahydro-β-carboline, m.p. 205–207°.

Anal. Calcd. for $C_{14}H_{17}N_2O$: C, 73.36; H, 7.42; N, 12.22. Found: C, 72.83; H, 7.20; N, 11.96.

2-Butyryl-6-methoxy-1-methyl-1,2,3,4-tetrahydro-β-carboline.—6-Methoxy-1-methyl-1,2,3,4-tetrahydro-β-carboline (100 mg., 4.6×10^{-4} mole) was dissolved in 0.5 ml. of butyric anhydride by heating, then adding 1.0 ml. of pyridine. The mixture was allowed to stand at room temperature for 24 hr. A small quantity of water was added; the oil that formed initially solidified after several days standing. The solid was obtained by decantation and crystallized from ethanol–water to yield 72 mg. (54%) of product, m.p. 118–122°. A portion was recrystallized for analysis, m.p. 122–127°.

Anal. Calcd. for $C_{17}H_{22}N_2O_2$: C, 71.29; H, 7.74; N, 9.80. Found: C, 71.29; H, 7.66; N, 9.79.

Reduction of 3,4-Dimethoxyphenylacetyl Chloride by the Rosenmund Method.—3,4-Dimethoxyphenylacetyl chloride was prepared by refluxing the acid with thionyl chloride in chloroform.[24] Several typical Rosenmund reductions were carried out exploring the variables of time and temperature on the reaction using either toluene or xylene as solvents. The progress of the reactions was monitored by bubbling the effluent gases first through a Dry Ice trap and then through standardized sodium hydroxide. It was then possible to calculate the amount of hydrogen chloride formed by titration of the base. The yield of the aldehyde was calculated on the basis of the amount of sodium bisulfite addition product formed from the reaction mixture. Details of one of the experiments are described below.

3,4-Dimethoxyphenylacetyl chloride (5 g., 0.02 mole) was dissolved in 25.0 ml. of toluene, and 0.5 g. of palladium-on-barium sulfate and 6 drops of a quinoline sulfur "poison" were added. The mixture was stirred and refluxed while admitting a stream of hydrogen through a fritted glass opening. The effluent gases were passed through a Dry Ice trap and through a bubbler containing 30 ml. of 1.17 *N* sodium hydroxide. Aliquots (2 ml.) were removed and titrated periodically, to indicate a 68% conversion of the acid chloride to hydrogen chloride at the end of 30 hr. The reaction was stopped, and the cooled mixture was filtered. Vigorous shaking of the clear filtrate with saturated sodium bisulfite solution overnight yielded 0.9 g. (13.6%) of the addition product. The derivative was treated with 10% sodium carbonate and evaporated to dryness; the residue was extracted with ethanol and filtered. Upon treating this filtrate, in the conventional manner with 2,4-dinitrophenylhydrazine, 0.16 g. of 3,4-dimethoxyphenylacetaldehyde 2,4-dinitrophenylhydrazone was obtained. One crystallization from ethanol yielded an analytical sample, m.p. 166–168°.

Anal. Calcd. for $C_{16}H_{16}N_4O_6$: C, 53.33; H, 4.02; N, 15.55. Found: C, 52.78; H, 4.41; N, 15.35.

The highest recovery of aldehyde (1.37 g., 17%) from the conditions tried was obtained at the end of 6 hr. in refluxing xylene. The greatest quantity of hydrogen chloride at (86% of the theoretical) was obtained after 24 hr. of hydrogenation at refluxing xylene temperatures, but none of the aldehyde could be isolated from that experiment.

3,4-Dimethoxyphenylacetaldehyde.—A superior method for this aldehyde was by the oxidation of 4-allylveratrole first to the glycol with potassium permanganate. The glycol then was cleaved oxidatively with lead tetraacetate to the desired aldehyde according to established procedures.[18]

1-(3,4-Dimethoxybenzyl)-6-methoxy-1,2,3,4-tetrahydrocarboline Hydrochloride.—Seven milliliters (7.7×10^{-3} mole) of a stock solution of 3,4-dimethoxyphenylacetaldehyde (1.3 g. aldehyde/7.0 ml. ethanol) and 1.0 g. (5.3×10^{-3} mole) of 5-methoxytryptamine were dissolved into 10.0 ml. of ethanol. Water (5 ml.) was added, and the pH was brought to 4 with *N* hydrochloric acid. After 4 days at room temperature under nitrogen, the white crystalline precipitate that formed was filtered to give 0.6 g. of product. Reduction of the volume of the filtrate yielded an additional 0.1 g. of the carboline hydrochloride to yield a total of 0.7 g. (35%) of crude product, m.p. 235–239°. Crystallization from ethanol yielded an analytical sample, m.p. 239–242°.

Anal. Calcd. for $C_{21}H_{25}ClN_2O_3$: C, 64.85; H, 6.48; N, 7.20. Found: C, 64.20; H, 6.50; N, 7.98.

1-(3,4-Dimethoxybenzyl)-1,2,3,4-tetrahydro-β-carboline Hydrochloride.—3,4-Dimethoxyphenylacetaldehyde (350 mg., 2.1 $\times 10^{-3}$ mole) was dissolved into 5.0 ml. of ethanol, and 4.0 ml. of water was added to obtain a slight cloudiness. Tryptamine hydrochloride (300 mg., 1.7×10^{-3} mole) was added together with 2 drops of 2 *N* sulfuric acid and 3.0 ml. more of ethanol to obtain a clear solution. The solution was allowed to stand at room temperature for 24 hr. and then was extracted with ether, discarding the ether extracts. Upon reduction of the volume of the aqueous portion, 210 mg. (34.4% yield), m.p. 232–238°, was obtained. A portion was crystallized from ethanol, m.p. 233–235°.

Anal. Calcd. for $C_{20}H_{23}ClN_2O_2$: C, 66.93; H, 6.46; N, 7.81. Found: C, 66.85; H, 6.60; N, 7.93.

1-Benzyl-1,2,3,4-tetrahydro-β-carboline was prepared from tryptamine and phenylacetaldehyde according to a known procedure.[17]

5-Methoxy-N-methyltryptamine.—Essentially, the method of Wilkinson[21] starting with 5-methoxytryptamine, ensuring monoalkylation by the attachment of a tosylate group, was used. The melting point (161–164°) of 5-methoxy-N-toluene-*p*-sulfonyltryptamine differed from the reported one (123–124°).

(24) R. D. Haworth, W. H. Perkin, and J. Rankin, *J. Chem. Soc.*, 1694 (1924).

Anal. Calcd. for $C_{25}H_{23}N_5O_5S_2$: N, 8.20; S, 9.30. Found: N, 8.15; S, 9.69.

Upon methylation with methyl iodide, however, a 5-methoxy-N-methyl-N-toluene *p*-sulfonyltryptamine whose melting point coincided with the literature value was obtained, m.p. 117–120° (lit.[21] m.p. 118–119°). It was then possible to convert this tosylate with liquid ammonia in good yield to a very pure, hitherto unreported, 5-methoxy-N-methyltryptamine base by modifying the literature procedure somewhat. Thus, instead of ether extraction of the water solution of the ammonia detosylation residue, the solid that precipitated was filtered, washed, and dried. In this manner 347 mg. (9.3×10^{-4} mole) of 5-methoxy-N-methyl-N-toluene-*p*-sulfonyltryptamine yielded 127 mg. (67%) of 5-methoxy-N-methyltryptamine, m.p. 99–102°.

Anal. Calcd. for $C_{12}H_{16}N_2O$: C, 70.55; H, 7.90; N, 13.72. Found: C, 70.41; H, 7.79; N, 13.50.

A picrate was prepared in the usual manner; 136 mg., m.p. 224–226° dec., was obtained from 75 mg. of the free base.

Anal. Calcd. for $C_{18}H_{18}N_5O_8$: C, 50.00; H, 4.19; N, 16.20. Found: C, 50.61; H, 4.51; N, 15.77.

5-Methoxy-2-oxo-2,3-dihydrotryptamine.—5-Methoxy-3-oxindolylacetonitrile was prepared starting from 5-methoxyisatin and cyanoacetic acid.[22] The nitrile (9 g., 0.045 mole) was hydrogenated in 100.0 ml. of ethanol and 9.0 ml. of concentrated hydrochloric acid over 0.5 g. of platinum oxide catalyst at 2.8 kg./cm.^{2} for 2.5 hr. The reaction mixture was filtered through Celite and all of the solvents were removed under vacuum. The product was crystallized from ethanol–chloroform. In several crops, a total of 5.8 g. (69% yield) of product was isolated. The crops varied in melting points from 270 to 275° with the first crop having the best purity, m.p. 275° dec.

Anal. Calcd. for $C_{11}H_{15}ClN_2O_2$: C, 54.39; H, 6.23; Cl, 14.61; N, 11.54. Found: C, 54.41; H, 6.22; Cl, 14.75; N, 11.47.

Serotonin Antagonism.—The myotropic response to a standard dose of 0.4 μg. of serotonin was determined using estrus rat uterus, in a muscle bath. The potency of compounds in the series was determined by the amount required to antagonize the action of the standard. If less than 5 μg. of compound was required for antagonism it was rated as 4+, 5–20 μg. as 3+, 20–50 as 2+, 50–100 μg. as +, more than 100 μg. as no activity. Results are given in Table I.

Effect on Behavior.—The effect of compounds on behavior was determined in the following manner. Rats were conditioned on a variable interval (V.I.) positive reinforcement schedule, *i.e.*, bar pressing in a Skinner box at a steady medium rate which was rewarded automatically with food pellets. Faster or slower rates therefore represented less reward for effort and would indicate that behavior was not optimal. Animals were deprived of food and spent 50 min. each day in the test chamber. The mean rate of response during each quarter of the test period on 5 consecutive days was determined. On the experimental day the compound was administered intraperitoneally, and the increased (+) or decreased (−) response rates were computed as a percentage of the normal. Many rats were used to determine the effect of each compound, and several dose levels were employed. Specific examples to illustrate the action of each compound are quoted in Table I.

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Acyltryptamines. III. 5-Acetyltryptophan and Related Compounds

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A number of 5-acetylindole derivatives, such as 5-acetyltryptophan, 5-acetylheteroauxin, 5-acetylskatole, 5-acetylgramine, 5-acetyl-N,N-dimethyltryptamine, 6-acetyl-1,2,3,4-tetrahydronorharman, various 1-substituted 6-acetyl-1,2,3,4-tetrahydro-β-carbolines, and 10-acetyl-17,18-dimethoxy-15,16,17,18,19,20-hexadehydroyohimbane were synthesized. Most of these compounds produced hypotensive effects in dogs.

The introduction of the acetyl group into position 5 of the tryptamine molecule results in a significant change in its pharmacological properties.[1] This finding suggested the preparation of 5-acetyl analogs of other indole-containing substances of physiological significance. The present investigation concerns itself with the synthesis of derivatives of gramine, skatole, N,N-dimethyltryptamine, tryptophan, heteroauxin, β-carboline, and yohimbane, which are substituted by acetyl groups in the position *para* to the indole nitrogen.

It has been shown in the course of this work that the acetyl group at C-5 of the indole nucleus can survive the conditions of catalytic –C–N– hydrogenolysis as well as a variety of acid- and base-catalyzed condensation reactions. A survey of the literature suggested that all of the desired compounds could be synthesized starting from 5-acetylgramine (I) and 5-acetyltryptamine (II). Our first task, therefore, centered upon the preparation of 5-acetylgramine. The problem was approached by two routes. One involved the formation of the indole nucleus in the course of the synthesis; the other utilized preformed 5-acetylindole as the starting material.

The first route was an adaptation of Hegedüs'[2] tryptophan synthesis which had the advantage of also being applicable to the synthesis of 5-acetyl-N,N-dimethyltryptamine (III). The synthetic scheme involved a Japp–Klingemann coupling of diazotized *p*-aminoacetophenone with ethyl α-(2-dimethylaminoethyl)acetoacetate (IV) and ethyl α-(3-dimethylaminopropyl)acetoacetate (V) to give the *p*-acetylphenylhydrazones of ethyl α-keto-γ-dimethylaminobutyrate (VI) and of ethyl α-keto-δ-dimethylaminovalerate (VII). Cyclization of the hydrazones with polyphosphoric acid gave 5-acetyl-2-carbethoxygramine (VIII) and 5-acetyl-2-carbethoxy-N,N-dimethyltryptamine (IX), respectively. However, decarbethoxylation of ester VIII as well as decarboxylation of 5-acetyl-2-carboxygramine (X), obtained by hydrolysis of VIII, proved to be very difficult. Heating with resorcinol,[3] sulfuric acid, or hydrobromic acid resulted solely in extensive decomposition, whereas prolonged refluxing in hydrochloric acid–acetic acid gave 5-acetylgramine (I) in a maximum yield of 2.5%.[4] The slow rate of decarboxylation of this compound is in

(1) (a) J. Shavel, Jr., M. von Strandtmann, and M. P. Cohen, *J. Am. Chem. Soc.*, **84**, 881 (1962); (b) M. von Strandtmann, M. P. Cohen, and J. Shavel, Jr., 141st National Meeting of the American Chemical Society, Washington, D.C., March, 1962.

(2) B. Hegedüs, *Helv. Chim. Acta*, **29**, 1499 (1946).

(3) H. Plieninger, *Ber.*, **83**, 268 (1950).

(4) Uncorrected for recovered acid X.