[CONTRIBUTION FROM THE ORGANIC CHEMICAL RESEARCH SECTION, PEARL RIVER LABORATORIES, RESEARCH DIVISION AMERICAN CYANAMID CO.]

3-Sulfanilamido-6-alkoxypyridazines and Related Compounds

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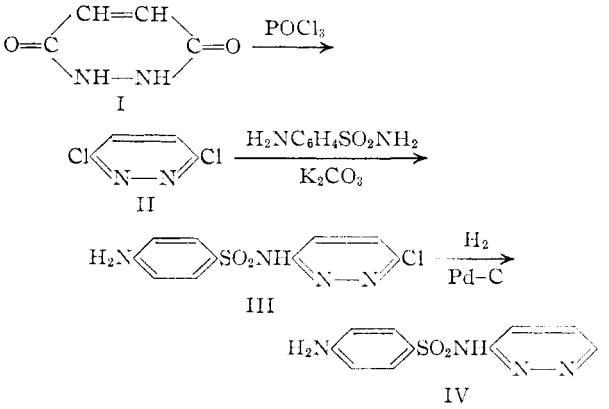
3-Sulfanilamido-6-chloropyridazine when reacting with the sodium derivatives of various alcohols or phenol gave the corresponding ethers. Related derivatives of 3-sulfanilamido-4- and 5-methylpyridazine also were prepared. 3-Sulfanilamido-6-methoxypyridazine is of the greatest interest because of its high antibacterial activity and slow excretion.

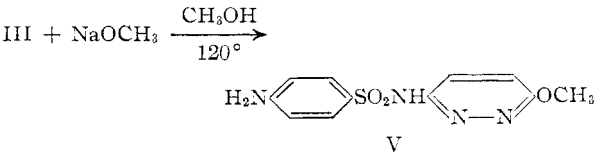
Recent developments in pyridazine chemistry have made rather readily available the hitherto difficultly prepared[1] 3-sulfanilamidopyridazine (IV). Maleic hydrazide (I) is readily converted by the action of phosphorus oxychloride into 3,6-dichloropyridazine (II).[2,3] This reactive intermediate can



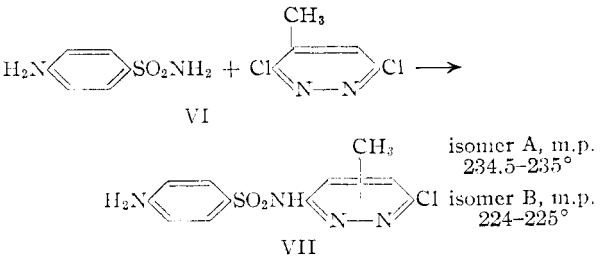
be converted into 3-sulfanilamido-6-chloropyridazine (III) by fusion with sulfanilamide and potassium carbonate.[3-5] The catalytic dehalogenation of this compound gives 3-sulfanilamidopyridazine (IV).[3,5,6] A longer synthesis of IV through 3-aminopyridazine[7] also has been reported.

Re-evaluation of the bacteriology and pharmacology of the latter compound gave results of sufficient interest to suggest the study of other sulfanilamidopyridazines such as those derivable from 3-sulfanilamido-6-chloropyridazine (III) and certain of its homologs.[8,9]

The reaction of III with sodium methoxide in methanol at 120° in an autoclave gave 3-sulfanilamido-6-methoxypyridazine (V).[10] Table I lists this compound and seven other ethers similarly obtained by the reaction of III with the sodium derivatives of the corresponding alcohols or phenol. The reaction conditions and yields are, in most cases, based on a single run and are probably not optimal. For the methyl homolog it was found that temperatures and times below those given resulted in incomplete reaction while higher temperatures gave a reaction mixture which was quite difficult to purify.



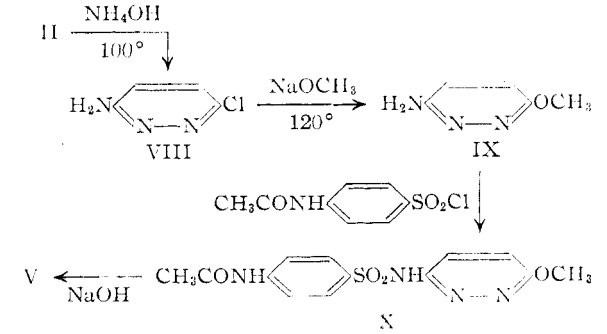
Two methyl homologs of 3-sulfanilamido-6-chloropyridazine were obtained by the reaction of 3,6-dichloro-4-methylpyridazine[4] with sulfanilamide.



It was found possible to separate, by fractional acidification of an alkaline solution, the mixture of isomers resulting from this reaction. Previous workers[4] have reported only a single product from the preparation of a sulfanilamide from VI.

Table II lists the properties of the isomers obtained from the above reaction and also the products obtained from these isomers by catalytic dehalogenation and by reaction with sodium methoxide.

An alternative synthesis of 3-sulfanilamido-6-methoxypyridazine (V) involved the reaction of 3-amino-6-chloropyridazine[4] (VIII) with sodium methoxide at 120°. The resulting 3-amino-6-



(1) P. S. Winnek and R. O. Roblin, Jr., U. S. Patent 2,371,115 (March 6, 1945); *C. A.*, **40**, 604 (1946); G. W. Anderson, H. E. Faith, H. W. Marson, P. S. Winnek and R. O. Roblin, Jr., THIS JOURNAL, **64**, 2902 (1942).

(2) R. H. Mizzoni and P. E. Spoerri, *ibid.*, **73**, 1873 (1951).

(3) M. M. Rogers and J. P. English, U. S. Patent 2,671,086 (March 2, 1954); *C. A.*, **49**, 1824b (1955).

(4) J. Druey, K. Meier and K. Eichenberger, *Helv. Chim. Acta*, **37**, 121 (1954).

(5) M. M. Rogers and J. P. English, U. S. Patent 2,712,011 (June 28, 1955); *C. A.*, **50**, 5776i (1956).

(6) M. M. Lester and J. P. English, U. S. Patent 2,790,798 (April 30, 1957).

(7) C. Grundmann, *Ber.*, **81**, 1 (1948).

(8) N. A. Kuck, "Sulfamethoxypyridazine in Bacterial Infections in Mice," presented at meeting of New York City Branch of Society of American Bacteriologists, January 15, 1957.

(9) R. R. Roepke and T. H. Maren, unpublished results.

(10) The trademark of the American Cyanamid Co. for this compound is Kynex.

TABLE I

SULFANILAMIDOPYRIDAZINES H_2N—⟨benzene⟩—SO_2NH—⟨pyridazine⟩—OR

R	Reaction Temp., °C.	Time, hr.	Yield, %	M.p., °C.	Molecular formula	Analyses, % Calculated C	H	N	Found C	H	N
CH_3	115–120	15	59	182–183	$C_{11}H_{12}N_4O_3S$[a]	47.1	4.3	20.0	46.9	4.6	20.0
C_2H_5	150	13	48	183–184	$C_{12}H_{14}N_4O_3S$	49.0	4.8	19.0	49.1	5.0	19.0
n-C_3H_7	150	13	20	184–185	$C_{13}H_{16}N_4O_3S$	50.6	5.2	18.2	51.0	5.2	18.5
i-C_3H_7	150	13	10	187–188	$C_{13}H_{16}N_4O_3S$	50.6	5.2	18.2	51.0	5.5	18.3
									50.6	5.6	
n-C_6H_{13}	150	40	29	140–141	$C_{16}H_{22}N_4O_3S$	54.8	6.3	16.0	54.6	6.4	16.1
$C_6H_5CH_2$	145	12	Trace	200–201	$C_{17}H_{16}N_4O_3S$	57.3	4.5	15.7	57.3	4.7	15.9
$C_6H_5CH_2CH_2$	220	2.5	30	173–174	$C_{18}H_{18}N_4O_3S$	58.4	4.9	15.1	58.1	5.0	14.7
C_6H_5	140	9	15	[b]	$C_{16}H_{14}N_4O_3S$	56.1	4.1	16.4	56.4	4.4	16.6

[a] Calcd. for CH_3O 11.1, found 10.8. [b] Melts at 139–140°; resolidifies and remelts at 160–161°.

TABLE II

6-SUBSTITUTED-3-SULFANILAMIDO-4(OR 5)-METHYLPYRIDAZINES H_2N—⟨benzene⟩—SO_2NH—⟨CH_3-pyridazine⟩—R

R	M.p., °C.	Molecular formula	Analyses, % Calculated C	H	N	Found C	H	N
		"A" Series						
Cl	234.5–235[a]	$C_{11}H_{11}ClN_4O_2S$[b]	44.2	3.7	18.8	43.9	3.8	18.6
OCH_3[f]	199–202[c]	$C_{12}H_{14}N_4O_3S$	49.0	4.8	19.0	48.9	5.0	19.0
H	270–273[d]	$C_{11}H_{12}N_4O_2S$	50.0	4.6	21.2	50.3	4.8	21.2
		"B" Series						
Cl	224–225	$C_{11}H_{11}ClN_4O_2S$[e]	44.2	3.7	18.8	44.2	3.8	18.3
OCH_3[f]	197–198.5	$C_{12}H_{14}N_4O_3S$	49.0	4.8	19.0	49.1	5.1	18.8
H	254–255 (sint. 249)	$C_{11}H_{12}N_4O_2S$	50.0	4.6	21.2	49.7	4.6	21.1

[a] Mixed m.p. with isomer 200–221°. [b] Cl, calcd. 11.9, found 12.0. [c] Mixed m.p. with isomer 170–185°. [d] Mixed m.p. with isomer 227–230°. [e] Cl, calcd. 11.9, found 11.6. [f] These compounds were prepared by M. J. Muller.

methoxypyridazine (IX) was converted, by reaction with acetylsulfanilyl chloride, to 3-N^4-acetylsulfanilamido-6-methoxypyridazine (X). Alkaline hydrolysis of this material gave a product identical with that obtained by the action of sodium methoxide on 3-sulfanilamido-6-chloropyridazine.

A number of observations have been made on the ease of replacement of the first of the two chlorines of 3,6-dichloropyridazine with a variety of reagents and also on the ease of reaction of sodium methoxide with several 3-chloropyridazines variously substituted in the 6-position. While some of these observations were suggestive, the studies were not sufficiently extensive or rigorous to permit valid generalizations.

The reaction of 3,6-dichloropyridazine with sodium sulfanilamide to produce 3-sulfanilamido-6-chloropyridazine requires a fusion at temperatures above 120° in the presence of potassium carbonate. When the reaction was attempted in refluxing methanol the only products isolated were methoxypyridazines. On the other hand, 3,6-dichloropyridazine reacts with one equivalent of sodium methoxide in methanol at room temperature with a vigorous exothermic reaction.[4]

It appears[4] that a temperature of 100° with pressure is required for the reaction of the dichloro compound with aqueous ammonia to produce 3-amino-6-chloropyridazine. No reaction was observed when ammonia gas was passed for several hours through a stirred aqueous supension of the dichloro compound at 90°.

In contrast with the ready reaction of sodium methoxide with a 3-chloropyridazine having another chlorine in the 6-position as noted above, it is necessary to reflux 3-chloro-6-methoxypyridazine for about eight hours with methanolic sodium methoxide to obtain a satisfactory yield of 3,6-dimethoxypyridazine.[11] Even these conditions, however, are not sufficient to bring about the reaction of 3-sulfanilamido-6-chloropyridazine or 3-amino-6-chloropyridazine with sodium methoxide. Both require a pressure reaction at 120° for 15 to 20 hours.

Of the compounds prepared 3-sulfanilamido-6-methoxypyridazine is the most interesting chemotherapeutically. The compound is equivalent to sulfadiazine in activity against experimental infections of mice[8] and is excreted very slowly.[12]

The solubilities of a number of the compounds reported in this paper as well as certain related sulfanilamidopyridazines were determined at 37° in buffers of various pH's. The values obtained are given in Table III. Details of the determinations are given in the Experimental part.

Experimental

Melting points were taken on a calibrated Fisher–Johns block. Analyses were carried out by the staff of the Microanalytical Laboratory of the Stamford Research Laboratories under the direction of Dr. J. A. Kuck. Infrared spectra were determined and interpreted under the super-

(11) The pressure reaction apparently used as a general method by Druey, *et al.*,[4] is unnecessary in this case.

(12) R. R. Roepke, T. H. Maren and E. Mayer, *Ann. N. Y. Acad. Sci.*, **69**, 457 (1957).

TABLE III

SOLUBILITY OF VARIOUS 3-SULFANILAMIDOPYRIDAZINES AT 37°

R	Source[c]	Solubility, mg./100 cc., at pH 5	6	7
3-Sulfanilamido-6-R-pyridazines				
H	A	155	380	400
Cl	B	60	165	700
OCH_3	C	110[a]	120[a]	147[a,b]
OC_2H_5	C	49	55	110
3-Sulfanilamido-4(or 5)-methyl-6-R-pyridazines				
Cl (isomer A)	C	12	15	133
Cl (isomer B)	C	17	76	193
H (from isomer A)	C	11	12	15
3-N^4-Acetylsulfanilamido-6-R-pyridazines				
H	C	36	47	165
Cl	C	18	80	360
OCH_3	C	35	40	75

[a] In acetate buffer; see Discussion. [b] pH 6.5. [c] A, see ref. 3–6. B, see ref. 3–5. C, see Experimental.

vision of Dr. R. C. Gore of the Stamford Research Laboratories.

3-Sulfanilamido-6-methoxypyridazine (V) from III.—A mixture of 150 g. (0.527 mole) of 3-sulfanilamido-6-chloropyridazine,[3-5] 77.2 g. (1.43 moles) of sodium methoxide and 20 g. of Darco S-51 was heated in a rocking autoclave for 15 hours at 115–120°. The cooled reaction mixture was filtered, stirred with Darco for an hour, filtered and made slightly acid with glacial acetic acid. The solution was evaporated at room temperature and the solid which separated was filtered, washed with water and recrystallized twice from methanol (about 1 g./10 ml.); m.p. 182–183°, yield 87 g. (59%). This material, in common with most of the sulfanilamidopyridazines reported here, had a pale yellow color that could not be removed.

3-Amino-6-methoxypyridazine (IX).—A solution of 3.4 g. (0.026 mole) of 3-amino-6-chloropyridazine[4,7] and the sodium methoxide from 0.61 g. (0.027 atom) of sodium in 30 ml. of methanol was heated in a bomb tube at 120° for 20 hours.[13] The resulting mixture was filtered to remove sodium chloride and the filtrate evaporated to dryness at room temperature. The residue was recrystallized from a 3:2 mixture of petroleum ether and chloroform (charcoal) and then from *n*-amyl chloride; yield 0.5 g. (15%), m.p. 103–105°.

Anal. Calcd. for $C_5H_7N_3O$: C, 48.0; H, 5.6; N, 33.6. Found: C, 47.7; H, 5.7; N, 33.7.

3-(N^4-Acetylsulfanilamido)-6-methoxypyridazine (X).

A. From IX.—To a solution of 0.29 g. (0.0023 mole) of 3-amino-6-methoxypyridazine (VIII) in 2 ml. of dry pyridine was added slowly with stirring at 50° a solution of 0.57 g. (0.0024 mole) of acetylsulfanilyl chloride in 1.5 ml. of dry pyridine. The resulting solution was maintained at 60° for 30 minutes and then poured into sufficient 0.1 *N* sodium hydroxide to give a final *p*H of 7. The solution was evaporated to dryness and the residue triturated with water. The insoluble solid was filtered and recrystallized from 75% aqueous methanol (charcoal) to give a material of m.p. 220.5–221.5°. The infrared spectra of this material and that described below were identical.

B. **From V.**—A slurry of 11.2 g. (0.04 mole) of 3-sulfanilamido-6-methoxypyridazine (V) in 50 ml. of 75% aqueous acetic acid was treated with 10.0 ml. (0.12 mole) of acetic anhydride. The mixture, which warmed spontaneously, was stirred for 20 minutes, chilled and filtered. After thorough washing with water and ether, 12.6 g. (98%) of a product of m.p. 221.5–222.5° remained. Crystallization from aqueous ethanol gave 10.2 g. (79%) of material melting 226–227°.

Anal. Calcd. for $C_{13}H_{14}N_4O_4S$: C, 48.4; H, 4.4; N, 17.4; CH_3O, 9.6. Found: C, 48.2; H, 4.4; N, 17.2; CH_3O, 8.5–9.3 (erratic).

(13) Only starting material was recovered after refluxing such a solution for 18 hours.

3-Sulfanilamido-6-methoxypyridazine from X.—A solution of 0.32 g. (0.001 mole) of 3-(N^4-acetylsulfanilamido)-6-methoxypyridazine, prepared by method A above, in 7.2 cc. of distilled water containing 0.80 g. (0.02 mole) of sodium hydroxide was refluxed for 45 minutes. Precipitation by acidification with dilute acetic acid gave 0.22 g. (79%) of 3-sulfanilamido-6-methoxypyridazine of m.p. 182.5–183.5°. The melting point of a mixture with the material prepared from III was not depressed.

3-Sulfanilamido-6-chloro-4(and 5)-methylpyridazines (VII, Isomers A and B).—A mixture of 33.6 g. (0.2 mole) of 3,6-dichloro-4-methylpyridazine[4] (VI), 51.0 g. (0.3 mole) of sulfanilamide, 49 g. (0.3 mole) of anhydrous potassium carbonate and 42 g. of sodium chloride was ground in a mortar and placed in a flask with a powerful stirrer. The stirred mixture was heated with a flame until the temperature reached 160° (reaction was evident at 140°). The temperature then rose to 180° without further heating. When the contents had cooled to 100°, about 150 ml. of water was added and the mixture boiled until no further solution occurred. The aqueous layer then was decanted from a heavy oil,[14] chilled and extracted with ether to remove 3.6 g. of unreacted 3,6-dichloro-4-methylpyridazine. The solution then was acidified to obtain a mixture of gum and solid which eventually solidified completely. The solid was filtered and dried to obtain 48.4 g. (81%) of crude mixed isomers, m.p. 190–198°.[15]

The solid was dissolved in dilute sodium hydroxide, treated with charcoal and the product fractionally reprecipitated by the addition of the calculated amount of acetic acid in eight equal portions. The attainment of equilibrium after each addition was quite slow and the mixture was stirred for at least seven hours after the acid was added before the resulting precipitate was filtered. The first two precipitates were negligible in amount and of poor quality and were discarded. The next three fractions, weighing a total of 18.9 g., melted within the range 232–235° and precipitated within the *p*H range 8.1–8.4 (fraction A). The last three fractions, weighing 23.7 g., precipitated over the *p*H range 6.0–8.0 and melted between 194 and 206° (fraction B).

Fraction A was dissolved in alkali, reprecipitated with acetic acid, and the resulting precipitate filtered and leached with hot 50% aqueous ethanol; yield 16.3 g. (27%), m.p. 234.5–235°. This compound will be referred to as "VII, isomer A."

Fraction B was recrystallized from glacial acetic acid to obtain 12 g. of material melting at 214–215°. An analytical sample was obtained by further recrystallization, with heavy losses, from ethyl acetate; m.p. 224–225° (VII, isomer B). A mixture with isomer A melted at 200–221°. The infrared spectra of the two materials showed marked differences throughout.

Preparation of Ethers Listed in Tables I and II.—The ethers listed in Table I were prepared from 3-sulfanilamido-6-chloropyridazine by a procedure basically similar to that described for 3-sulfanilamido-6-methoxypyridazine. The conditions of time and temperature given for the methoxy compound were established as optimal after the other work had been done. Their use would probably have given better yields of the other ethers.

The ethers listed in Table II were prepared similarly from the isomeric 3-sulfanilamido-6-chloro-4(or 5)-methylpyridazines (VII; see above).

3-Sulfanilamido-4(or 5)-methylpyridazine from VII; Isomer A.—A solution of 1 g. (0.0035 mole) of 3-sulfanilamido-6-chloro-4(or 5)-methylpyridazine (VII, isomer A) in 10 ml. of 4% aqueous sodium hydroxide was treated with 100 mg. each of 10% palladium–charcoal and 10% platinum–charcoal. The solution was shaken with hydrogen at a pressure of four atmospheres for 90 minutes. The catalyst was filtered and the product precipitated by pouring the filtrate into dilute acetic acid. The solid was filtered

(14) This oil solidified on chilling. It was found to be impure sulfanilamide (m.p. 143–144°). It also contained 2.5 g. of unreacted 3,6-dichloro-4-methylpyridazine which was recovered by extraction of the recovered sulfanilamide with ether.

(15) Druey, *et al.*, reported a melting point of 210–214° for a related material. It is not clear from their paper whether their product was prepared by our method or from 3-amino-4(or 5)-methyl-6-chloropyridazine. It also is not clear whether any attempt to separate isomers was made.

and purified by extracting three times with 50% aqueous alcohol. The very small amount of insoluble product melted at 270–273°.

3-Sulfanilamido-4(or 5)-methylpyridazine from VII; Isomer B.—This isomer was prepared and purified as described for the compound derived from isomer A; m.p. 254–255° (sintering from 249°). A mixture with the isomer melting at 270–273° melted at 227–230°. The infrared spectrum of this compound showed marked differences throughout from that of the isomer melting at 270–273°.

Preparation of 3-N⁴-Acetylsulfanilamidopyridazines.—The following compounds were prepared by procedure B described above for the 6-methoxy compound X.

3-N⁴-Acetylsulfanilamidopyridazine was obtained from 3-sulfanilamidopyridazine[3,6] in 90% yield, m.p. 204–205° (from aqueous alcohol). *Anal.* Calcd. for $C_{12}H_{12}N_4O_3S$: C, 49.3; H, 4.1; N, 19.2. Found: C, 49.5; H, 4.3; N, 19.3.

3-N⁴-Acetylsulfanilamido-6-chloropyridazine was obtained in the same way from the corresponding sulfanilamide III[3-6] in 96% yield, m.p. 224–225°. *Anal.* Calcd. for $C_{12}H_{11}ClN_4O_3S$: C, 44.1; H, 3.4; N, 17.2; Cl, 10.9. Found: C, 44.3; H, 3.6; N, 17.0; Cl, 10.6.

Solubilities.[16]—Solubilities of various sulfanilamidopyridazines and their N⁴-acetyl derivatives were carried out at 37° by the general method of Biamonte and Schneller.[17] Determinations in duplicate of each of duplicate samples were made. Only values from such determinations that agree within 5% are reported. Equilibration was demonstrated either by the agreement of values determined at 24-hour intervals or of values from samples brought to 37° from both room temperature and 95°. Excess solid phase was present at all times and constant stirring or shaking was employed.

Citrate–phosphate buffers were used in all but one case. 3-Sulfanilamido-6-methoxypyridazine did not give reproducible results in this buffer. It was necessary in this case to use an acetate buffer (0.1 *M*) to obtain equilibrium values that agreed. The highest practical *p*H obtainable with this buffer was 6.5.

(16) We are indebted to J. J. Licari and D. S. Davies for carrying out many of these determinations.

(17) A. R. Biamonte and G. H. Schneller, *J. Am. Pharm. Assoc., A (Scient. Ed.)*, **41**, 341 (1952).

PEARL RIVER, N. Y.

[CONTRIBUTION FROM THE NATIONAL INSTITUTE OF ARTHRITIS AND METABOLIC DISEASES AND THE NATIONAL HEART INSTITUTE, NATIONAL INSTITUTES OF HEALTH]

Oxindole Analogs of (5-Hydroxy)-tryptamine and -tryptophan, as Inhibitors of the Biosynthesis and Breakdown of Serotonin[1]

BY K. FRETER, H. WEISSBACH, B. REDFIELD, S. UDENFRIEND AND B. WITKOP

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Tryptamine and O-benzylserotonin were converted to the corresponding oxindole derivatives IIa, IIb, IIc *via* the symmetric disulfides Ia, Ib. As a result of interaction of the basic amino group with the lactam carbonyl of the oxindole ring, milder alkaline hydrolysis than required for unsubstituted oxindoles opened IIa to α-(*o*-aminophenyl)-γ-aminobutyric acid (V), characterized as the dicarbobenzyloxy derivative IV, which on debenzylation gave back V, and reclosed on attempted recrystallization to IIa and, as shown by electropherograms (Fig. 1), another compound possibly the isomeric pyrrolidone VI. IIa showed good competitive inhibition of the destruction of serotonin in a purified soluble monamine oxidase system; its action in intact rats, however, decreased from 100% after 15 minutes to 25% after 4 hours, when tested in liver homogenates of the sacrificed animals. IIa also inhibited 5-hydroxytryptophan decarboxylase *in vitro* as did several other oxindole derivatives of which 2,5-dihydroxytryptophan was the most active.

Recent interest in the possible role of serotonin in brain function has focused attention on the enzymes involved in the biosynthesis and metabolism of this new amine. This investigation reports the effects of oxindole analogs of (5-hydroxy)-tryptophan and -tryptamine on 5-hydroxytryptophan (5-HTP) decarboxylase and monamine oxidase (MAO).

A. Chemistry of 3-(β-Aminoethyl)-oxindoles.—The activation of peptide bonds by suitably located amino or hydroxyl groups under proper enzymatic or non-enzymatic catalysis leads to N → O acyl migration and hydrolysis, or to N → N *trans*-peptidization. Interesting recent model rearrangements of this type are the conversion of diglycinimide to glycylglycine at *p*H 5[2,3] or the alkali-catalyzed transformation of O-glycylsalicylidipeptide esters to salicyltripeptide esters.[4]

As part of an investigation on oxindolylalanine peptides the chemical part of this paper describes the synthesis of oxindole-β-ethylamines (IIa, b, c) in which the basic amino group interacts with the lactam carbonyl of the oxindole ring in analogy to similar intramolecular reactions in the oxindole series.[5]

The synthesis of 2-hydroxytryptamine by the alkylation of an unsubstituted oxindole with chloroacetonitrile and subsequent hydrogenation is not possible.[6] Hendrickson[7] was able to condense ethyl hippurate with oxindole to the largely enolic (VIIb) β-hippuryloxindole (VIIa), whose catalytic reduction in the presence of acid led to III in 90% yield. The hydrolysis of III proved difficult and gave a complicated mixture of compounds from which IIa could not be isolated. We introduced the 2-oxy function directly into tryptamine by mild reductive acid hydrolysis of the symmetric disulfide Ia, a reaction utilized before with pyrroles,[8] tryptophan[9] and lysergic acid diethylamide.[10] The use of N-carbobenzyloxytryptamine (see Experimental part) offered no advantages.

(1) Presented in part at the Conference on the Biochemistry of Mental Disease, University of British Columbia, Vancouver, B. C., June 16–18, 1957.

(2) Th. Wieland, E. Bokelmann, L. Bauer, H. V. Lang and H. H. Lau, *Ann.*, **583**, 129 (1953).

(3) Th. Wieland, H. V. Lang and D. Liebsch, *ibid.*, **597**, 227 (1955); *cf.*, Th. Wieland, *Angew. Chem.*, **69**, 362 (1957).

(4) M. Brenner, J. P. Zimmermann, J. Wehrmüller, P. Quitt and I. Photaki, *Experientia*, **11**, 397 (1955); M. Brenner, *Angew. Chem.*, **69**, 102 (1957).

(5) E. Wenkert and Th. L. Reid, *Experientia*, **10**, 417 (1954).

(6) E. Wenkert, private communication.

(7) James B. Hendrickson, Thesis, Harvard University, 1954.

(8) H. Fischer and M. Herrmann, *Hoppe-Seyler's Z. physiol. Chem.*, **122**, 4 (1922).

(9) Th. Wieland, O. Weiberg, E. Fischer and G. Hörlein, *Ann.*, **587**, 146 (1954).

(10) K. Freter, J. Axelrod and B. Witkop, THIS JOURNAL, **79**, 3191 (1957).