central part of the molecule by the attachment of two, rather than one, five-membered ring systems. The virtual identity of the two molecules of the asymmetric unit is evident from the dihedral angles of the C–S–S–C bridges, which were calculated to be 15.2 and 18.2°, respectively. The two molecules are oriented in such a way that their disulfide bridges are nearly parallel, and facing each other. The packing forces seem to consist largely of van der Waals attractions; however, the possibility of some d orbital overlap between two sulfur atoms of adjacent molecules is indicated by a short S–S nonbonded interaction of 3.27.[6]

A more detailed account of this structure determination will be published at a later date.

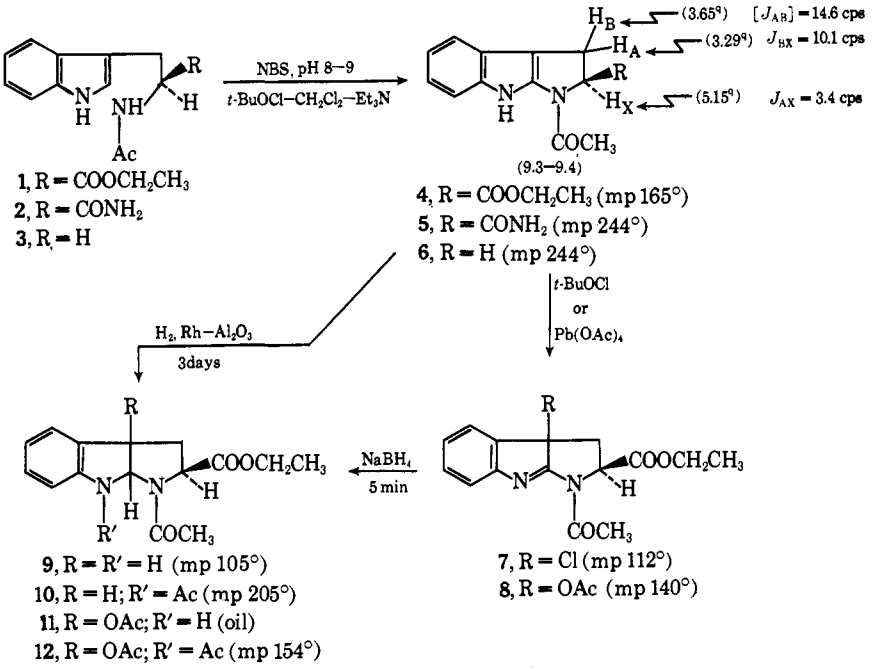
(6) A similar distance (3.29 Å) was observed in 4-methyl-1,2-dithia-4-cyclopentene-3-thione: W. L. Kehl and G. A. Jeffrey, *Acta Cryst.*, **11**, 813 (1958), and G. A. Jeffrey and R Shiono, *ibid.*, **12**, 447 (1959).

D. B. Cosulich, N. R. Nelson, J. H. van den Hende
American Cyanamid Company, Lederle Laboratories Division
Pearl River, New York 10965
Received June 28, 1968

Cyclization of Tryptophan and Tryptamine Derivatives to Pyrrolo[2,3-*b*]indoles

Sir:

Although the conversion of tryptophan and tryptamine to tricyclic pyrroloindoles has been discussed in connection with oxidation mechanisms,[1] the ring-chain tautomers of tryptamine (serotonin),[2] and (bio)synthesis of alkaloids of the physostigmine type[3] and of the antibiotic sporidesmin,[4] no laboratory method for this important conversion has been available. We wish to report several useful approaches which make easily accessible cyclic tryptophan derivatives of type **4**–**13**.



1, R = $COOCH_2CH_3$
2, R = $CONH_2$
3, R = H

4, R = $COOCH_2CH_3$ (mp 165°)
5, R = $CONH_2$ (mp 244°)
6, R = H (mp 244°)

9, R = R′ = H (mp 105°)
10, R = H; R′ = Ac (mp 205°)
11, R = OAc; R′ = H (oil)
12, R = OAc; R′ = Ac (mp 154°)

7, R = Cl (mp 112°)
8, R = OAc (mp 140°)

While N-acyltryptophan derivatives with N-bromosuccinimide (NBS) at pH 4 yield spirooxindole-(imino)lactones, presumably *via* bromonium or β-bromoindolenine intermediates,[5] the same reaction carried out with N-acetyltryptophan ethyl ester (**1**) in 0.04 *M* phosphate, pH 9.2, with exactly 1 equiv of NBS (1.6×10^{-2} *M*) in very dilute solution (5×10^{-4} *M*) at room temperature yields an unstable product (60% yield on the basis of uv absorption) which had been recognized previously by its characteristic λ_{max}, 308 mμ[6] (ε 15,700). Since excess NBS or hydrolysis at or below pH 6 converts this product into a (bromo)-oxindole, it has to be extracted immediately into ether. The crystalline product (30% yield) has the composition $C_{15}H_{16}N_2O_3$, mol wt 272.1166 (calcd 272.1161). Structure **4**, ethyl 1-acetyl-2,3-dihydropyrrolo[2,3-*b*]-indole-2-carboxylate, is supported by the nmr data (in parentheses), by the uv absorption which resembles that of 2-acetamidoindole,[7] and by the easy hydrolysis to an oxindole. In the same way the carboxamide **5** was prepared from **2**, while the much slower oxidation of N-acetyltryptamine (**3**) led to N-acetyldehydrotryptamine (**6**) in solution only.

The pyrroloindole **4** was obtained in 80% yield by oxidation of a solution of N-acetyltryptophan ethyl ester (**1**) with *t*-BuOCl in methylene chloride containing a threefold excess of triethylamine. The same method made the cyclic tryptamine **6** easily available in 63% yield, when the reaction mixture, presumably containing the 3-chloroindolenine intermediate, was treated with 1 equiv of ethanolic NaOH.

The pyrroloindole **4** was slowly reduced over a $Rh–Al_2O_3$ catalyst in ethyl acetate (3 days) to 2,3,3a,8a-tetrahydropyrroloindole (**9**) (30% yield). The sharp doublet in the nmr spectrum at δ 5.70 ppm (J = 7 cps), characteristic of the 8a proton, was absent when **4**

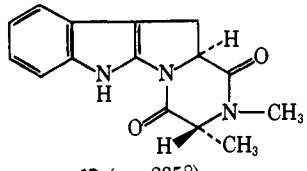
(1) A. Ek, H. Kissman, J. B. Patrick, and B. Witkop, *Experientia*, **8**, 36 (1952).
(2) I. I. Grandberg, T. I. Zujanova, N. I. Afonina, and T. A. Ivanova, *Dokl. Akad. Nauk SSSR*, **176**, 583 (1967).
(3) B. Witkop and R. K. Hill, *J. Amer. Chem. Soc.*, **77**, 6592 (1955).
(4) *Cf.* A. F. Beecham, J. Friedrichsons, and A. M. Mathieson, *Tetrahedron Lett.*, 3131 (1966).
(5) B. Witkop, *Advan. Protein Chem.*, **16**, 221 (1961).
(6) N. M. Green and B. Witkop, *Trans. N. Y. Acad. Sci., Ser. II*, **26**, 659 (1964). The appearance of the 308-mμ peak in peptides and proteins is dependent on environmental factors and secondary structure.
(7) J. Kebrle and K. Hoffmann, *Helv. Chim. Acta*, **39**, 116 (1956).

was reduced with deuterium. Acetylation of **9** with Ac_2O in pyridine gave **10**.

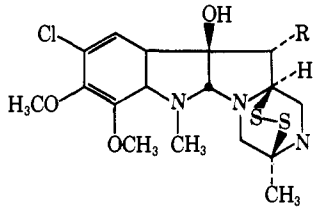
Further action of *t*-BuOCl on **4** at −10° gave the unstable 3a-chloroindolenine (**7**) in 57% yield. Analogously, 1 equiv of lead tetraacetate in CH_2Cl_2 gave the 3a-acetoxyindolenine (**8**) (23% yield) which was rapidly reduced by $NaBH_4$ in CH_3OH at 0° to the 3a-acetoxyindoline **11**, characterized as the diacetyl derivative **12**.

The diketopiperazine from L-tryptophyl-N-methyl-L-alanine reacted at 0° with 1.1 mol of *t*-BuOCl and Et_3N in a mixture of methylene chloride–dimethoxyethane (2:1, v/v) to yield 51% of the tetracyclic pyrroloindole **13**, a suitable model whence to explore approaches to sporidesmins A (**14**) and B (**15**).[4]

When the 3a-chloroindolenine **7** was refluxed in absolute ethanol with excess sodium acetate, the fully aromatic ethyl pyrrolo[2,3-*b*]indole-2-carboxylate (mp 186–188°, $\lambda\lambda_{max}^{EtOH}$ 330, 272 mμ) was obtained. This new tricycle, unlike **4**–**6**, is stable to acid. This great stability is also supported by preliminary delocalization energy calculations for the parent tricycle.[8]



13 (mp 235°)



14, R = OH
15, R = H

(8) We are obliged to Dr. K. Kirk for th s information.

(9) Associate in the Visiting Program of the U. S. Public Health Service, 1966–1968.

Motonori Ohno,[9] Thomas F. Spande, Bernhard Witkop
National Institute of Arthritis and Metabolic Diseases
National Institutes of Health, Bethesda, Maryland 20014
Received July 3, 1968

Photocyclizations of Pharmacodynamic Amines. II. X-Ray Analysis of a Noncentrosymmetric Tetracyclic Indole

Sir:

The photolysis of N-chloroacetyl derivatives of aromatic amino acids and pharmacodynamic amines so far has led to tricyclic indoles, benzazepines, and azaazulenes.[1]

We have now found two novel photocyclizations of the N-chloroacetyl derivative of 3,4-dimethoxyphenethylamine, the catatonic compound implied as a metabolite in schizophrenia (I).[2] On irradiation *in ethanol–water solution* with a 100-W mercury lamp for 1.5 hr at room temperature, the cyclization reaction, in analogy with that of N-chloroacetyldopamine,[1] yielded the two isomeric benzazepines III and IV.

In addition a deep-seated photorearrangement gave a product, mp 123.5°, in 10–12% yield, for which structure V, *i.e.*, one arbitrarily chosen antipode, 1,2,-5a,7bβ-tetrahydro-5aβ,5bα-dimethoxy-5bH-cyclobuta-[1,4]cyclobuta[1,2,3-*gh*]pyrrolizin-4(5H)-one, of the racemic photoproduct, was established.

An X-ray diffraction analysis of a single optically active crystal, picked out of the racemic conglomerate, has established the structural formula and the configuration of the photoproduct. Eleven hundred independent reflections were recorded with Cu radiation by the multiple-film, equiinclination Weissenberg technique. The space group is $P2_12_12_1$ with four molecules per unit cell and the cell parameters are a = 11.75 Å, b = 6.27 Å, and c = 14.70 Å. Phases for the strong and moderately strong reflections were determined directly from the experimental intensities by the symbolic addition procedure[3] for noncentrosymmetric crystals. In the initial density map computed with 306 reflections whose phases had been determined, the positions of the 13 strongest peaks suggested an unusual arrangement of atoms. The coordinates of the 13 peaks were used as a partial structure in a recycling procedure employing the tangent formula, and the remaining three carbon atoms were located. Hydrogen atoms were found in a difference map. A least-squares refinement of the coordinates and thermal parameters has reached an agreement factor of 10.0%. In this way structure V was deduced with the bond lengths and angles illustrated in Figure 1.

On heating with alumina in toluene V aromatizes with loss of the elements of methanol to the lactam 2-oxo-8-methoxy-1,2,4,5-tetrahydropyrrolo[3,2,1-*hi*]indole (XI) which has almost the same chromophore [$\lambda\lambda_{max}$ mμ (ε): 301 (4630), 254 (6030); 219 (20,500)] as the indole alkaloid schizogalin.[4] Under the conditions of Fischer esterification the lactam V is opened to the ester hydrochloride X, from which base regenerates V.

On the other hand, irradiation of the amine I *in tetrahydrofuran solution* under the conditions described above gave the novel ten-membered lactam VI, 12-methoxy-2-oxa-6-azabicyclo[7.3.1]trideca-1(13),9,11-trien-5-one, as the major product, in addition to II, III, IV, V, and recovered I (Chart I). On heating in 48% hydrobromic acid at 140° for 2 hr, VI was converted to the tricyclic 9-hydroxy-2,3,5,6-tetrahydropyrano[2,3,4-*ij*]isoquinoline hydrobromide (VII).

The O-methyl ether VIII was also obtained from VI by cyclization with 6.0 *N* HCl at room temperature for

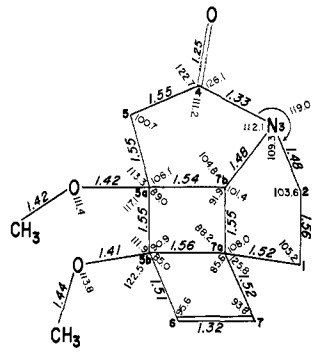


Figure 1. Bond distances and angles of compound V. Additional angles about atoms 5a, 5b, and 7a are as follows: 6–5b–5a, 114.6°; O–5b–7a, 126.0°; 5b–5a–5, 116.1°; O–5a–7b, 111.9°; 1–7a–5b, 127.0°; 7–7a–7b, 115.9°.

(1) *Cf.* O. Yonemitsu, T. Tokuyama, M. Chaykovsky, and B. Witkop, *J. Am. Chem. Soc.*, **90**, 776 (1968).

(2) *Cf.* C. R. Creveling and J. W. Daly, *Nature*, **216**, 190 (1967).

(3) I. L. Karle and J. Karle, *Acta Cryst.*, **17**, 835 (1964); J. Karle and I. L. Karle, *ibid.*, **21**, 849 (1966); **B24**, 182 (1968).

(4) U. Renner and P. Kernweisz, *Experientia*, **19**, 244 (1963).