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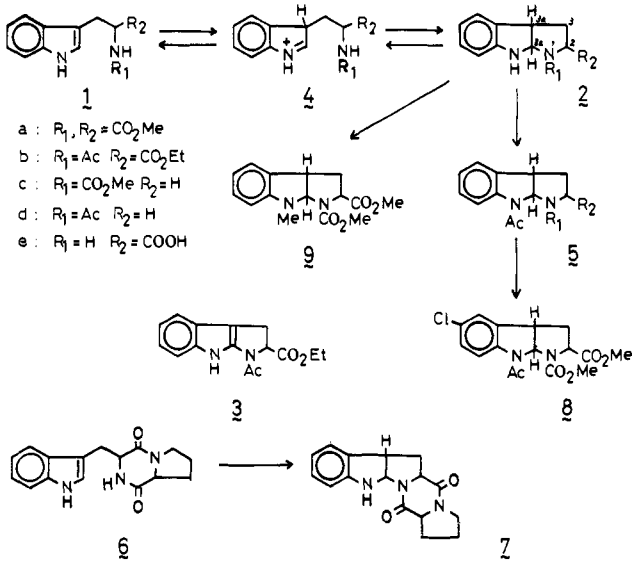
Cyclic Tautomers of Tryptophans and Tryptamines. 1. Formation and Reactions

Sir:

1,2,3,3a,8,8a-Hexahydropyrrolo[2,3-*b*]indoles **2** have been considered as possible tautomers of tryptamines and tryptophans **1**. The NMR spectra of tryptamines in deuteriochloroform have been studied, but no measurable amount of the tautomer has been observed.[1] Tryptamines and tryptophans were later shown to be protonated at the indole 3 position as well as the N_b position in strong acid; however, the acid-catalyzed cyclization to **2** was not observed.[2,3] More recently, the formation of a cyclic tautomer of tryptophan **2e** has been postulated as a possible intermediate for the selective enzymatic prenylation of tryptophan.[6] However, a study of the reactivity of indoline tautomers of type **2** has been hindered by the lack of a general method for their synthesis. To our knowledge, the only available precedent is the preparation of **2b** by Witkop and co-workers using a catalytic hydrogenation of **3** prepared from *N*-acetyltryptophan ethyl ester and *tert*-butyl hypochlorite.[7]

We report here the first direct synthesis and reactions of tryptophan and tryptamine cyclic tautomers. When N_b-methoxycarbonyl-DL-tryptophan methyl ester **1a** was dissolved in 85% phosphoric acid at ambient temperature for 3 h followed by neutralization,[8] the pyrroloindole **2a**, mp 104.5–106.5 °C, was obtained as stable crystals in 85% yield. The structure of **2a** was supported by the following spectroscopic data: λ_{max} (EtOH) 243 nm (ϵ 7100), 299 (2400); IR (KBr) 3380, 1763, 1718, 1608 cm^{-1}; mass *m/e* 276 (M^+); ^1H NMR δ ($CDCl_3$) 2.57 (m, 2 H, 3-CH_2), 3.14, 3.16 (two s, 3 H, CO_2Me), 3.66, 3.79 (two s, 3 H, NCO_2Me), 3.9 (m, 1 H, 3a-H), 4.5 (m, 1 H, 2-H), 4.8, 5.15 (br, 1 H, NH), 5.49, 5.53 (two d, J = 6 Hz, 1 H, 8a-H), 6.5–7.1 (m, 4 H, arom H).[9,10]

Dissolving **1a** in 70–85% sulfuric acid, 50–85% sulfuric acid in methanol, or trifluoroacetic acid also generated the new cyclic tautomer **2a**, whereas **2a** was not obtained in concentrated sulfuric acid or formic acid. Although **2a** is stable in crystalline form at room temperature, it reverted to **1a** on heating or dissolving in methanol containing hydrochloric acid at room temperature. Similarly, *N*-acetyl-L-tryptophan ethyl ester (**1b**) was dissolved in 85% phosphoric acid and converted to the corresponding tautomer **2b**, mp 121–123 °C, in 29% yield. This was identical (mixture melting point, IR, and NMR) with a sample prepared by Witkop's procedure, providing strong support for the structure of the cyclic tautomer. Both **2a** and **2b** were isolated as single isomers. It was possible, however, to demonstrate the presence of the other isomer regarding the relative positions of the hydrogens at C-2 and C-3a by NMR spectra as well as TLC when the reaction of **1a** in 70% sulfuric acid in methanol was quenched after 15 min.



Although isolation of the other isomer was unsuccessful owing to its facile ring opening to **1a**, direct acetylation of the reaction mixture from **1a** with acetic anhydride followed by chromatography provided **5a** (the less stable isomer), mp 177–178.5 °C, in 30% yield and **5a** (the more stable isomer), mp 162–163.5 °C, in 51% yield. The N_a-acetyl derivative **5a** was found to be more stable than **2a**, but also readily underwent ring opening to give **1a** by acid treatment. The foregoing results suggest that the cyclization of **1** in acidic media may initially provide equal amounts of the two C-3a diastereoisomers via **4**. The less stable isomer, however, is converted readily into the more stable one through the open-chain isomer **4** in equilibrium with the cyclic tautomer **2**. This equilibrium has been demonstrated by exchange of the C-3a and C-8a protons in the NMR spectrum of **2a** in 85% deuteriophosphoric acid.[11]

This cyclization is applicable to a wide range of tryptophan tryptamine derivatives. Thus, a diketopiperazine (**6**) and the tryptamine carbamate **2c** were converted into cyclic tautomers **7**, mp 172 °C (dec), in 89% yield and **5c** via **2c**, mp 126.5–128 °C, in 71% yield, respectively.[12]

The cyclic tautomers **2** and **5** can be regarded as protected forms of the corresponding indoles. Electrophilic substitution at the 2 position is blocked and they are expected to react as indolines toward electrophiles. Electrophilic substitution of **2** or **5** should therefore provide a simple method for the preparation of tryptophan derivatives carrying a substituent on the benzene ring, since the cyclic tautomer is easily reconverted to the open-chain tautomer. This was found to be the case; thus, reaction of **5a** with *N*-chlorosuccinimide in acetic acid gave the 5-chloro derivative **8**, mp 157.5–159.5 °C, in 93% yield, which was converted to 5-chloro-N_b-methoxycarbonyltryptophan methyl ester in 89% yield on treatment with methanolic sulfuric acid. Finally, methylation of **2a** with methyl iodide in acetone–potassium carbonate gave the N_a-methyl derivative **9**, identical with a sample obtained by dissolving N_b-methoxycarbonyl-1-methyltryptophan methyl ester in 85% phosphoric acid.

Further reactions of **2** and **5** along these lines are now in progress.

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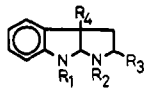
(3) The preparation of 3a-methylpyrrolo[2,3-*b*]indole derivatives (I) has been well documented in connection with physostigmine. We have recently developed a simple synthesis of 3a-hydroperoxy- or 3a-hydroxypyrroloindole derivatives (ii) by the dye-sensitized photooxygenation of tryptamines[4] and tryptophans.[5]



i) $R_4 = CH_3$

ii) $R_4 = OH$ or OOH

iii) $R_1 = H$ $R_2, R_3 = CO_2Me$ $R_4 = OH$

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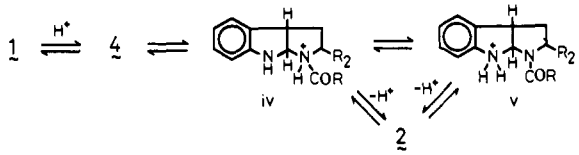
(8) The excess acid should be quenched by way of pouring the mixture into a mixture of 10% sodium carbonate and methylene chloride in an ice bath.

(9) The NMR spectrum showed the presence of two rotamers due to hindered rotation around the carbamate N–C bond. A similar spectrum was obtained in pyridine-d_5 at 25 °C, becoming a simple spectrum at 80 °C.

(10) The stereochemistry of the stable isomer **2a** is not established unequivocally, but comparison of its spectral data and its rate of N_a-acetylation with those of the *cis*- and *trans*-3a-hydroxypyrroloindole derivatives (iii),[5] whose structures (see note 3) have been established by X-ray analysis, indicates trans with respect to the 3a hydrogen and the ester group configuration for the stable isomer **2a**.

(11) The conversion of isomers may proceed via iv and v. The N_a-protonated form (v) was found to be a major species from the uv spectrum of 2 in 85% phosphoric acid. Deuterium exchange was observed not only at the 3a and 8a hydrogens, but also at benzene ring hydrogens of **2a**. Cf. S. Kang, T. H. Witherup, and S. Gross, *J. Org. Chem.*, **42**, 3769 (1977).



(12) N_b-Acetyltryptamine in 85% phosphoric acid, on the other hand, gave a dimeric product related to the skatole dimer as the main product. Tryptamine itself behaves similarly. These results indicate that the tautomerization to **2** competes with the dimerization. Furthermore, the nucleophilicity of the carbamate group seems to be greater than that of acetamido group in acidic media.

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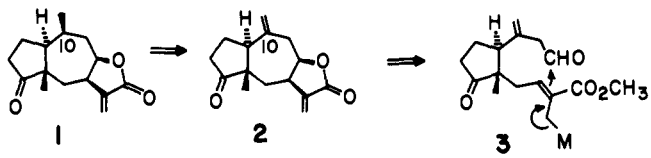
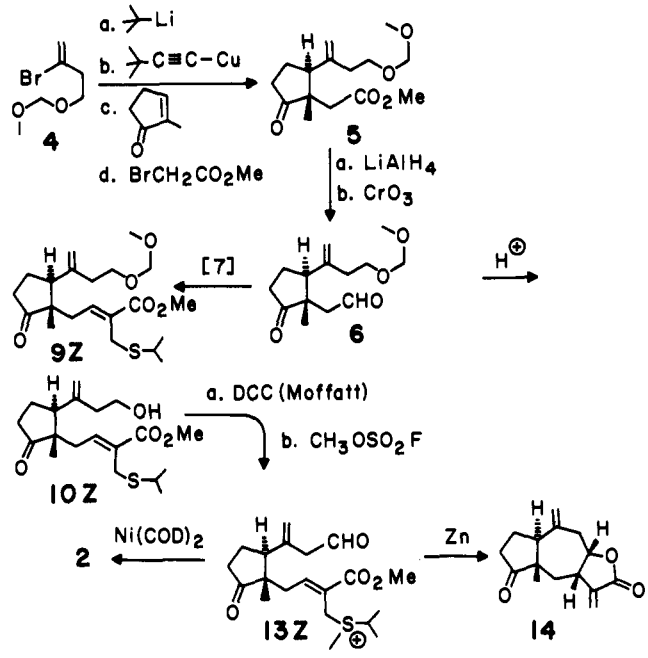
Total Synthesis of Confertin via Metal-Promoted Cyclization–Lactonization

Sir:

Confertin (**1**) is one of the simplest of the sesquiterpene α-methylene-γ-lactones, a class of compounds which have attracted attention as synthesis targets because of general cytotoxicity.[1] This member of the pseudoguaianolide family of sesquiterpenes has been the object of a successful total synthesis[2] and the closely related structure, damsin, has been prepared by three research groups.[3] In common with all previous syntheses of natural α-methylene-γ-lactones, the strategy



Scheme I



in these efforts involved addition of an α-methylene group to a carefully constructed γ-butyrolactone derivative.[4] We wish to report a new approach to sesquiterpene α-methylene-γ-lactones which we demonstrate with the total synthesis of confertin. Our strategy involves intramolecular coupling of an allylic metal species (e.g., **3**) with an aldehyde unit (cyclization) followed by spontaneous lactonization, making use of the natural functionality of the α-methylene carbonyl unit to facilitate formation of the allyl metal intermediate. The method is based on simple intermolecular examples of α-methylene-γ-lactone formation using allylzinc[5] and allylnickel[6] intermediates, and on our own model studies for intramolecular applications.[7]

Confertin (**1**) has five centers of chirality which have been assigned as shown based on spectral and chemical correlation with other natural sesquiterpene lactones.[8] Our strategy relies on selective hydrogenation of a C-10 *exo*-methylene group (in **2**) to introduce the proper stereochemistry at C-10, and selectivity for the β-cis lactone ring fusion from cyclization of **3** to **2**. The model studies[7] indicated a strong tendency for formation of cis ring fusion, but there was no obvious rational for predicting β-cis (natural) or α-cis lactone ring fusion. We entered into the synthesis of confertin partly to establish the stereochemical preferences for the cyclization–lactonization and to probe for control over stereoselectivity through the reaction variables implicit in general intermediate **3**. Scheme I presents the successful route, showing all isolated intermediates.[9] Vinyl bromide **4** was obtained from 4-hydroxy-1-butyne using the method of Boeckman.[10] Following the general strategy of organocuprate conjugate addition–enolate trapping,[11] vinyl bromide **4** was combined with 2-methyl-2-cyclopentenone and methyl bromoacetate to produce **5**. Halogen–metal exchange of **4** with *tert*-butyllithium followed by addition of (3,3-dimethyl-1-butynyl)copper(I)[12] gave an organocuprate to which was added 2-methylcyclopentenone at −45 °C. The resulting enolate in tetrahydrofuran–ether (1:4) was added to a 5-fold excess of methyl bromoacetate in ether–hexamethylphosphoric triamide (1:1, v:v) at −20 °C.[13] The product (**5**) was obtained in 85% yield, contaminated with <5% of the epimer (at C-5, pseudoguainolide numbering). The stereochemistry of **5** is as expected,[14] supported by ^1H NMR[15] and confirmed by the structure of the final product **1**.

The side-chain ester in **5** was converted to an aldehyde by

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