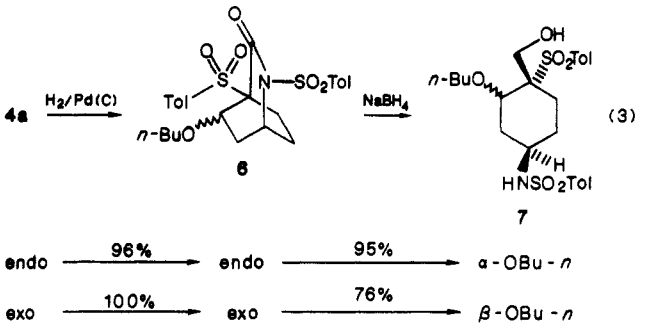
We expect that using alkyl vinyl ethers in which the alkyl group is bulkier than ethyl or *n*-butyl will lead to even higher endo:exo ratios in the cycloadducts. Cycloadducts **4a** and **4e** are richly functionalized, bridged, bicyclic lactams that should undergo a variety of chemoselective and stereoselective operations. For example, hydroxylation of the olefinic bond in these unsaturated lactams and opening of the lactam bridge would produce trioxygenated aminocyclohexanes structurally related to some antibiotic aminocyclitols.[13] As preliminary evidence that such unsaturated bicyclic lactams can be manipulated efficiently, cycloadducts *endo*-**4a** and *exo*-**4a** were separately catalytically hydrogenated to produce bicyclic lactams *endo*-**6** and *exo*-**6**, which were reductively cleaved by sodium borohydride[14] to form polyfunctionalized cyclohexanes 7α and 7β (eq 3).



Analysis of the 400-MHz ^{1}H NMR spectra of cyclohexyl butyl ethers 7α and 7β supported the stereochemical assignment of the major isomer as 7α and therefore the major cycloadduct **4a** as *endo*-**4a**, as expected in analogy to our results in the corresponding 3-sulfonyl-2-pyrone cycloadditions.[2,3] Specifically, isomer 7α showed a ^{1}H NMR peak for C*H*OBu at δ 3.73 with a width at one-half height ($W_{1/2}$) of 7.3 Hz characteristic of an equatorial hydrogen atom,[15,16] whereas isomer 7β (in which the more stable chair conformation has three equatorial substituents including the *n*-butoxy group) showed a peak at δ 4.02 (dd, J = 7.87, 3.77 Hz) with $W_{1/2}$ = 12.2 Hz.

We intend to apply these sulfonylpyridones to asymmetric cycloadditions in order to prepare aminocyclohexanols of high enantiomeric purity.

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Supplementary Material Available: Experimental details for preparation of **3**–**7** and spectroscopic and analytical data (21 pages). Ordering information is given on any current masthead page.

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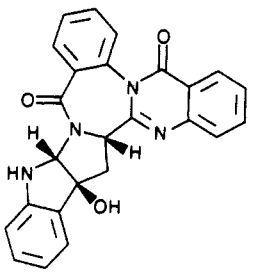
Total Synthesis of Nonpeptidal Cholecystokinin Antagonists from *Aspergillus alliaceus*†

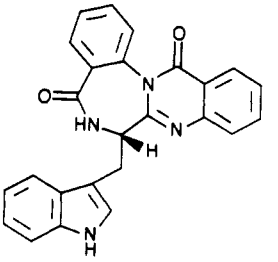
Summary: Two quinazolino-1,4-benzodiazepines isolated from *Aspergillus alliaceus*, which are antagonists of the peptide hormone cholecystokinin, have been synthesized from L-tryptophan and anthranilic acid.

Sir: Cholecystokinin (CCK), a 33-amino acid neuropeptide,[1] is a hormonal regulator of gall bladder contractility and of pancreatic enzyme secretion.[2] The discovery of the wide distribution of this gastrointestinal hormone in the brain[3] has aided in formulating the hypothesis that it may also function as a neurotransmitter or neuromodulator in the central nervous system.[4] Thus, CCK has been implicated in a variety of physiological functions such as satiety sensation,[5] sedation,[6] and analgesia.[7]

In this paper, we report the synthesis of two agents (**1** and **2**), isolated from a microbial source,[8] which are receptor antagonists of CCK.[9] These compounds are conceivably related biogenetically to the recently described CCK antagonist, asperlicin,[10] and constitute two additional examples of an emerging group of nonpeptidal compounds which are now recognized to be ligands for peptide hormone receptors.[11,12] The chemical structures of the title compounds **1** and **2** were deduced spectroscopically.



1



2

Our synthetic strategy for preparing **1** was based on the premise that it could be derived via intramolecular oxidative cyclization of **2**. Further disconnections of strategic bonds in **2** revealed that it, in turn, could be simplified to anthranilic acid and L-tryptophan. While alternative analyses can be envisioned, this plan suggested an approach which could be readily tested and, importantly, would afford intermediates which could be diverted to other synthetic objectives.

Reaction of isatoic anhydride **3** with L-tryptophan in water, in the presence of triethylamine, afforded the corresponding *N*-anthranoyl-L-tryptophan derivative (Scheme I). All volatile materials were then removed under reduced pressure and, without isolation of the intermediate, the resulting residue was heated in glacial acetic acid to give the benzodiazepinedione **4** (90% overall).[13,14] Further elaboration of **4** to give **2** required a regioselective annulation with anthranilic acid. This was accomplished in three steps by first reacting **4** with the Lawesson reagent[15] in tetrahydrofuran to give **5**[14] (33%) and an equivalent amount of the readily separable regioisomeric thionamide. The thionamide **5** was then transformed with iodomethane under phase-transfer conditions to the corresponding methyl imino thioether **6** (74%). In the final step, a mixture of crystalline **6** and methyl anthranilate was heated (neat) for 1 h to give **2** in 83% yield.[14,16] These

† Dedicated to Professor George Büchi on the occasion of his 65th birthday (J.P.S., R.M.F.).

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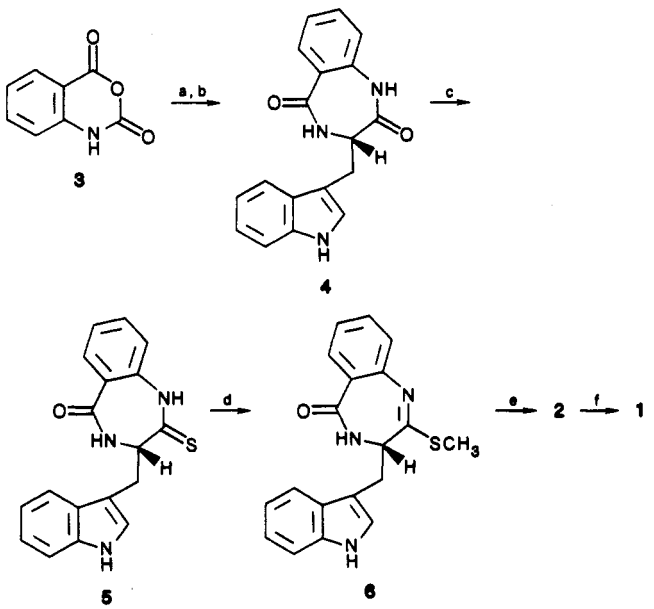
Scheme I[a]



[a] (a) L-Trp, NEt_3, H_2O, 23 °C, 5 h; (b) HOAc, 118 °C, 5 h (90% from 3); (c) $(CH_3OC_6H_4)_2P_2S_4$, THF, 23 °C, 2 h (33%); (d) CH_3I, $(n\text{-}Bu)_4NHSO_4$, NaOH (40%), $PhCH_3$, 23 °C, 20 min, (74%); (e) methyl anthranilate, 135 °C, 1 h, 83%; (f) $^1O_2$, rose bengal, CH_3OH–pyridine (5%), 0 °C, 5 h (32%).

conditions proved optimum, as slight deviations in temperature and time or modifications of the reagents resulted in incomplete reaction, decomposition, and/or racemization. Synthetic **2** was identical in all respects with an authentic sample obtained from the fermentation process.[17]

With the quinazolinobenzodiazepine **2** in hand, the following protocol was devised for transforming this material into **1**. Rose bengal sensitized photooxygenation of **2** in methanol–pyridine (5%) at 0 °C, using a 200-W halogen lamp, afforded a mixture of 3-hydroperoxyindolines.[18] The crude cyclization product was then reduced in situ with dimethyl sulfide to give a 32% yield of **1**, as confirmed by direct comparison with the authentic natural product.[17] Also isolated from the reaction mixture was a 28% yield of **7** (Figure 1), the corresponding diastereomer of **1**, in which the newly formed ring junction is cis and the hydroxyl group is α. The structure of this product was unambiguously established by single-crystal X-ray analysis,[19] thereby also verifying the spectroscopic structural assignments of **1** and **2**, respectively.

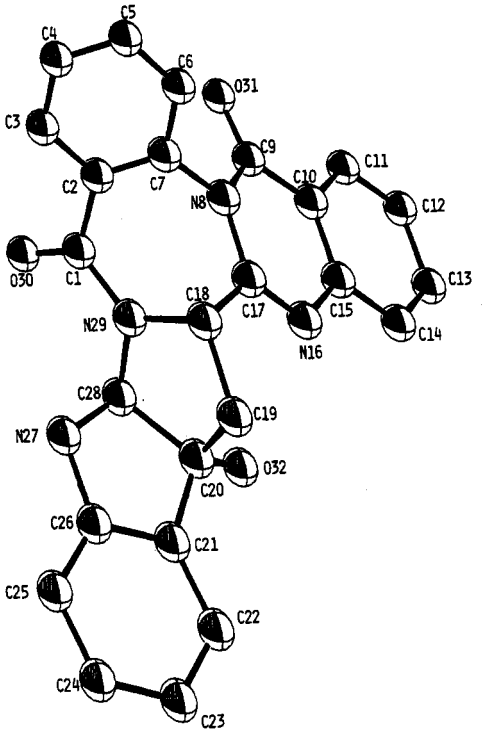


Figure 1. A computer-generated drawing of **7** derived from X-ray coordinates with hydrogens omitted for clarity.

These studies represent the first total syntheses of members of the asperlicin family of natural product CCK antagonists. Reports on our current efforts directed toward the synthesis of related structures, including asperlicin itself, will be forthcoming.

Acknowledgment. It is a pleasure to acknowledge the assistance of J.-P. Moreau, J. Smith, and S. Varga for analytical support. We thank Dr. M. A. Goetz for providing us with authentic samples of **1** and **2** and Dr. B. E. Evans for stimulating discussions. We are indebted to Drs. D. F. Veber and P. S. Anderson for support and encouragement.

Supplementary Material Available: Tables containing final fractional coordinates, temperature parameters, bond distances, and bond angles of **7** (7 pages). Ordering information is given on any current masthead page.

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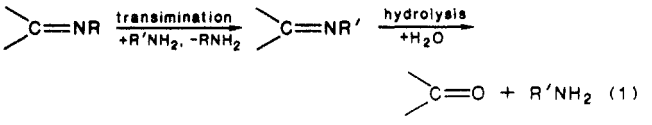
Intramolecular Base Catalysis in *N*-Benzylideneaniline Transimination by (Dimethylamino)alkylamines in Methanol[1]

Summary: The internal tertiary amino group in 2-(dimethylamino)ethylamine and 3-(dimethylamino)propylamine catalyzes proton transfer between nitrogen atoms of the *gem*-diamines formed in the course of the title reaction.

Sir: Recently, Okuyama et al.[2] reported that certain groups of amines catalyze the hydrolysis of *N*-(2-methoxybenzylidene)-2-methoxyethylamine through transimination and that this catalysis is very efficient when bifunctional amines carrying internal tertiary amino groups are used. This latter behavior was ascribed to intramolecular acid–base catalysis of (i) the initial transimination step and of (ii) the hydrolysis of the intermediate Schiff base formed (eq 1). Okuyama's results prompt us to



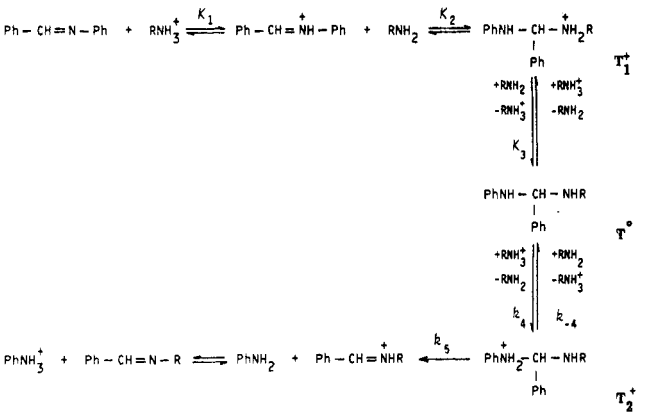
report that we have observed similar intramolecular base catalysis when studying transimination of *N*-benzylideneaniline (1) by (dimethylamino)alkylamines *directly* in methanol (eq 2).

$$\mathrm{PhCH{=}NPh} + \mathrm{H_2N(CH_2)_nNMe_2} \rightarrow \mathrm{PhCH{=}N(CH_2)_nNMe_2} + \mathrm{PhNH_2} \quad (2)$$

$$n = 2 \text{ or } 3$$

General catalysis of the Schiff base transimination reaction by acids and bases has been attributed to their promotion of the partly rate-limiting proton transfer between the two nitrogen atoms of the *gem*-diamine intermediate.[3] Despite the gem position of the two nitrogen atoms, proton transfer cannot occur intramolecularly by direct jump, but usually requires the intervention of a base, or acid, with intermediate formation of T^0 or T^{2+}, the neutral or diprotonated forms of the *gem*-diamine. When proton transfers from or to nitrogen atoms are fast enough, it is asssumed that the step which limits the rate is that which corresponds to the attack or expulsion of the less basic amine molecule. Because it is also expected that the partly rate-limiting proton transfer is that immediately adjacent to the attack or expulsion of the less basic amine,[3,4] and because the strong acidity of T^{2+} should make

Scheme I



the acid-catalyzed pathway inefficient, the rate should depend both on the protonation/deprotonation step to/from T_2^+ and on aniline cleavage from the same ionic species (Scheme I).

N-Benzylideneaniline transimination by propylamine (**2a**), 2-methoxyethylamine (**2b**), 2-(dimethylamino)-ethylamine (**2c**), and 3-(dimethylamino)propylamine (**2d**) was followed by UV spectroscopy, the absorbance decrease at 270 nm being monitored in methanol containing different buffer concentrations of free amine (RNH_2) and of the corresponding conjugate acid (RNH_3^+).[5] As expected from the above mechanism, the observed first-order rate constants, k_ψ, are linearly dependent on $[RNH_3^+]$ at constant amine concentration. In the case of monofunctional amino compounds, **2a** and **2b**, the second-order rate constants k_{II} ($k_\psi/[RNH_3^+]$) also depend on free amine concentration, with a leveling-off effect at high concentration (Figure 1). Since free amine concentration effects should cancel out if proton transfer were fast relative to aniline expulsion, this behavior can easily be accounted for by base catalysis of the T_1^+ to T_2^+ process by the amine itself. According to the above mechanism, k_ψ can be expressed by eq 3, and the second-order rate constant can be written as in eq 4. By plotting $1/k_{II}$ vs. $1/[RNH_2]$, excellent linear

$$k_\psi = \frac{K_1K_2K_3k_4k_5[RNH_3^+][RNH_2]}{k_{-4}[RNH_2] + k_5} = k_{II}[RNH_3^+] \quad (3)$$

$$\frac{1}{k_{II}} = \frac{k_{-4}}{K_1K_2K_3k_4k_5} + \frac{1}{K_1K_2K_3k_4[RNH_2]} = \frac{1}{(k_{II})_{max}} + \frac{k_5}{k_{-4}(k_{II})_{max}[RNH_2]} \quad (4)$$

relationships are observed with intercepts corresponding to $1/(k_{II})_{max}$ (the reciprocal of the asymptotic second-order rate constant at high amine concentration, i.e., when the rate is completely controlled by aniline expulsion). The ratios between slopes and intercepts give k_5/k_{-4} values of 0.060 M and 0.105 M for **2a** and **2b**, respectively.

In contrast to monofunctional amino compounds, the second-order rate constants k_{II} were found to be independent of amine concentration in the case of **2c** and **2d**, i.e., for amines carrying a tertiary group (Figure 1). Moreover, it is noteworthy that the mean value observed for **2c** (Table I), whose pK_a is very close to that of **2b**, does not differ significantly from the asymptotic maximum

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