BICYCLOANNULATION OF 3-INDOLYLENAMINES WITH CYCLOHEXENONE: A FACILE PREPARATION OF POTENTIAL NEUROTRANSMITTER ANALOGS

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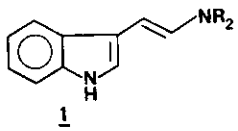
Abstract- Enamines of 3-indolylacetaldehyde undergo bicycloannulation with cyclohexenone to yield disubstituted bicyclo[2.2.2]octanones, and the mechanistic implications of the product stereochemistry are discussed. Wolff-Kishner reduction gives the corresponding disubstituted bicyclo[2.2.2]octane. Preliminary screening shows that these compounds may exhibit activity as neurotransmitter analogs.

Indolyl-substituted enamines such as 1 and 2 are interesting synthetic intermediates, since they contain three nucleophilic reactive sites (the β-carbon of the enamine, and C-3 and C-2 of the indole), and they possess the basic structural features (indole-C-C-NR_2 for 1, and indole-C-NR_2 for 2) of many naturally occurring alkaloids such as are found in the Aristotelia, Kopsia, and Aspidosperma families.



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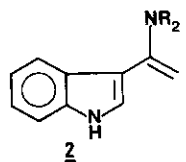

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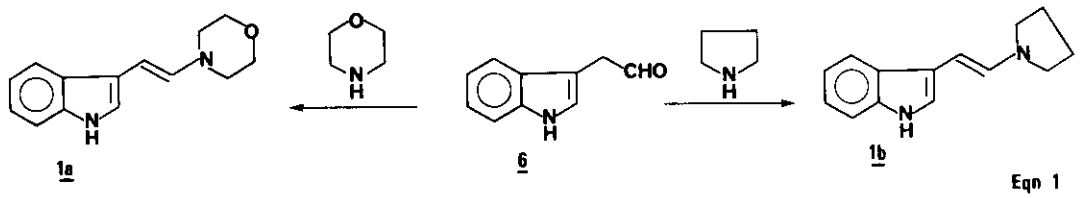
With the appropriate substitution, indolylenamines 1 and 2 should exhibit a useful spectrum of reactivity, since the nucleophilic functions could operate either independently, in concert or in opposition. Several derivatives of 1 have been prepared before,[1] but compounds of this type are otherwise little known. Our synthetic program has led us to explore the chemistry of such intermediates, and we report here a facile bicycloannulation reaction between enamines of type 1 and cyclohexenone (3) to yield the disubstituted bicyclo[2.2.2]octanones **4a-c**. Wolff-Kishner reduction of either **4b** or **4c** gives the corresponding bicyclo[2.2.2]octane 5. These adducts bear structural similarities to the putative central nervous

system neurotransmitter serotonin. Compounds such as these which can act as conformationally rigid analogs are of interest in the study of synaptic function, and could possess interesting medicinal properties.[2]

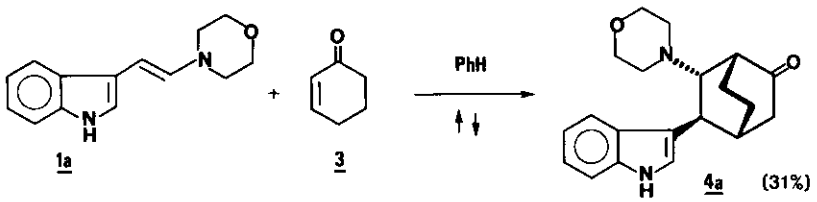
The unstable indole-3-acetaldehyde, **6**, is obtained by the oxidative decarboxylation of tryptophan,[3] and can be stored as the bisulfite adduct until needed. Enamines **1a,b** can be prepared readily from aldehyde **6** and morpholine or pyrrolidine in ether over molecular sieves at room temperature (Equation 1). The E stereochemistry of the enamines is supported by their ^{1}H-nmr spectra (J=13.5 Hz for indole-CH=CH-NR_2).



1a **6** **1b**

Eqn 1

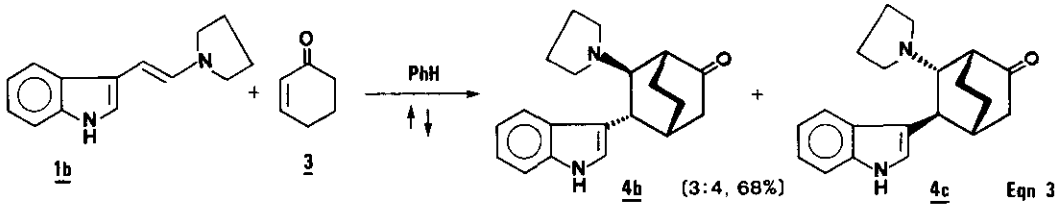
The reaction of the morpholine enamine **1a** with **3** in benzene at reflux led to an adduct for which was assigned the exo structure (2S,3R)-2-(3-indolyl)-3-(1-morpholinyl)bicyclo[2.2.2]octan-5-one, **4a**. Only one of the four possible stereoisomers was isolated as the major product after chromatography (Equation 2). The cis relative stereochemistry between the amino group and the carbonyl is assigned by analogy to the structure of the related adduct obtained by Singh and Rao, which was determined by X-ray diffraction.[4]



1a **3** **4a** (31%)

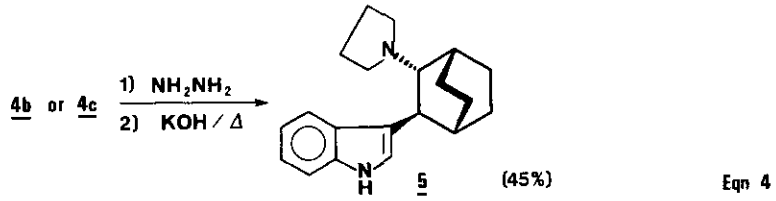
Eqn 2

The reaction of enamine **1b** with cyclohexenone gave a mixture of two products, for which the structures were assigned as the endo and exo structures (2R,3S)- and (2S,3R)-2-(3-indolyl)-3-(1-pyrrolidinyl)bicyclo[2.2.2]octan-5-ones **4b** and **4c**, which could be separated by chromatography (Equation 3). Two of the four possible stereoisomers are isolated, and these are assigned the two trans configurations on the basis of the ^{13}C-nmr spectra, and the subsequent deoxygenation. The ^{13}C-nmr spectrum of one of the adducts, **4c**, was very similar to that of the morpholine adduct **4a**, and the same relative stereochemistry is assigned for these two pro-



ducts.[4] In order to test for interconversion, each of the pure isomers **4b** and **4c** was heated to reflux in benzene for 12 h, but no crossover was detected.

Wolff-Kishner reduction of each of the isomers **4b** and **4c** separately under standard conditions gave the identical product, (2S,3R)-2-(3-indolyl)-3-(1-pyrrolidinyl)bicyclo[2.2.2]octane, **5** (Equation 4). This establishes the same relative stereochemistry of the amino and indolyl substituents in the adducts **4b,c**.

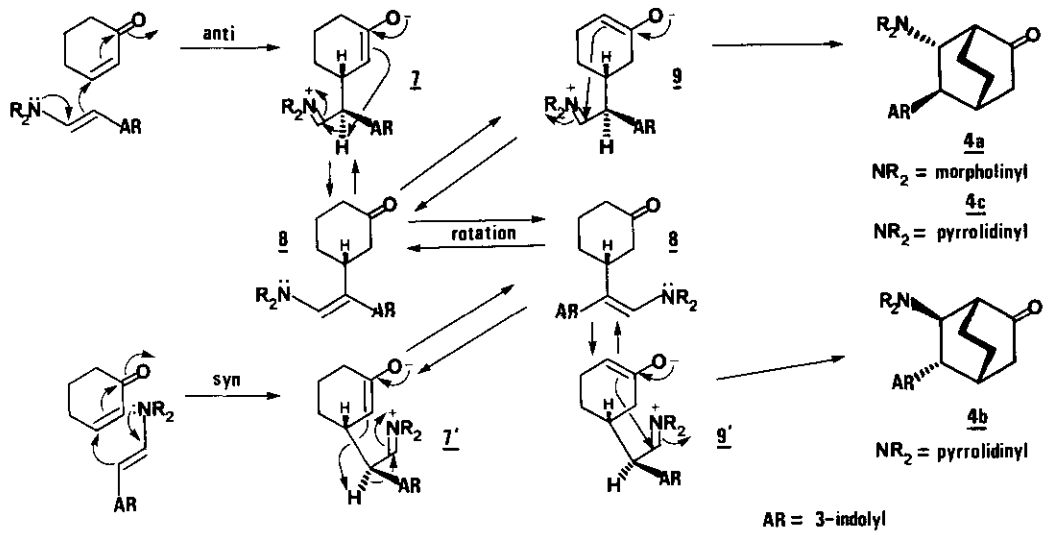


Initial attempts to react the enamine **1b** with other enones failed. With isophorone, 2-methylcyclohexenone or mesityl oxide, the enamine decomposed and the unreacted enone was recovered. The reaction with methyl vinyl ketone led to a complex mixture of products which were not further characterized.

Bicycloannulations of this type have been reported before,[4] as have cyclizations which involve an electrophilic two-carbon partner and the enolate or enamine of cyclohexenone[5] (i.e. the umpolung of the present reaction). The stereochemistry of the products has not previously been addressed within the context of mechanism.

These annulations may be viewed formally as concerted [4+2] cycloadditions between the indolylenamine and the cross-conjugated enol of cyclohexenone, but it is more probable that they occur by sequential Michael addition and Mannich reaction. We assume that the transition state for the Michael addition involves a parallel planes arrangement of the enone O=C-C=C and the enamine N-C=C, for maximum overlap. This can occur with these two moieties oriented either anti (exo) or syn (endo) with respect to each other,[6] and these two modes of addition would produce the diastereomeric zwitterionic intermediates **7** and **7'**, respectively. Proton

transfer in either intermediate via ketoenamine 8 gives rise to the regioisomeric enolates (i.e. 7 → 8 → 9 or 7' → 8 → 9'), and these latter undergo Mannich closure to yield the adducts 4a and 4c, or 4b, respectively.



The interesting mechanistic question is why the morpholine enamine 1a gives one isomer, while two result from the pyrrolidine enamine 1b. Our control experiments rule out equilibration between 4b and 4c, so the divergence could occur either at the stage of initial addition (anti vs syn), or during the proton transfer steps. Although the present data do not permit a distinction between these two possiblities, a better case can be made for the second interpretation.[7]

Pyrrolidine enamines are known for their increased reactivity and decreased stereoselectivity with respect to other enamines.[8] This behavior is ascribed to a stronger orbital interaction by the nitrogen lone pair, which is manifest in the ability of pyrrolidine enamines more readily to assume the immonium tautomeric form. In this case, the enolate immonium intermediate would be lower in energy, and the Mannich closure might be slow enough to allow the intermediate ketoenamine to rotate so that anti addition could lead to intermediate 9' in the syn series.

Molecules such as adducts 4 are of interest as rigid analogs of naturally occurring neurotransmitters,[2] and some compounds of this kind display antidepressant activity.[9] Preliminary pharmacological testing indicates that both 4b and 4c act as inhibitors of presynaptic imipramine binding and of serotonin uptake in mouse cerebral cortex preparations. We are pursuing the preparation of analogs of 4 for further testing.[10]

EXPERIMENTAL

Preparation of Enamines **1**: A solution of 0.867 g (3.30 mmol) of indole-3-acetaldehyde sodium bisulfite adduct in 40 ml of water was treated with saturated aqueous sodium carbonate until the solution became turbid. This solution was extracted with a total of 200 ml of ether, and the combined ether extracts were dried ($MgSO_4$) and concentrated to give 230 mg of indole-3-acetaldehyde (**6**). This was dissolved in 15 ml of anhydrous ether and was treated with 270 mg (3.10 mmol) of morpholine and the resulting mixture was stirred over molecular sieves at room temperature for 1 day. The solution was filtered through Celite and concentrated at high vacuum with gentle warming to yield 320 mg (100% from aldehyde) of enamine **1a** as a viscous yellow oil: ir ($CHCl_3$) 3460, 3100, 3000, 2970, 2860, 2830, 1645 cm^{-1}; ^{1}H-nmr ($CDCl_3$) δ 2.5 (4H,m), 3.35 (4H,m), 5.30 (1H,d,J=13.5 Hz), 6.18 (1H,d,J=13.5 Hz), 6.53 (1H,s), 6.78 (1H,br s), 7.3 (1H,m). Enamine **1b** was prepared likewise from pyrrolidine in 99% crude yield: ir ($CHCl_3$) 3450, 3100, 2955, 2860, 2820, 1640 cm^{-1}; ^{1}H-nmr ($CDCl_3$) δ 1.60 (4H,m), 2.63 (2H,t,J=6 Hz), 2.98 (2H,t,J=6 Hz), 5.06 (1H,d,J=13.5 Hz), 6.68 (1H,d,J=13.5 Hz), 7.40 (6H,m).

Preparation of Adducts **4**: A solution of 850 mg (4.01 mmol) of enamine **1b** in 15 ml of benzene was treated with 600 mg (6.25 mmol) of cyclohexenone (**3**), and this was heated to reflux under argon for 22 h. The crude product was purified by chromatography (20 g silica, hexane-ethyl acetate 3:1 v/v) to yield 364 mg (29%) of adduct **4b** and 482 mg (39%) of adduct **4c** as off-white solids: For **4b**: mp 199-200°C (ethyl acetate); ir (KBr) 3400, 3130, 3050, 2925, 2870, 2800, 1700 cm^{-1}; ^{1}H-nmr ($CDCl_3$) δ 1.68 (8H,m), 2.01 (1H,m), 2.23 (2H,m), 2.39 (4H,m), 2.71 (2H,m), 3.32 (1H,m), 6.87 (1H,d,J=1.7 Hz), 7.0-7.4 (3H,m), 7.58 (1H,m), 8.50 (1H,br s); ^{13}C-nmr ($CDCl_3$) δ 16.5, 23.1 (2), 25.6, 34.5, 39.8, 41.4, 49.1, 52.9 (2), 65.8, 111.3, 118.5, 119.1, 119.3, 120.8, 122.3, 126.8, 136.6, 217.6; mass spec. (high res. elec. impact, m/Z). Found: 308.1902. Calcd for $C_{20}H_{24}N_2O$: 308.1889. For **4c**: mp 180-183°C (ethanol); ir (KBr) 3400, 3130, 3040, 2935, 2860, 2800, 1700 cm^{-1}; ^{1}H-nmr ($CDCl_3$) δ 1.63 (5H,m), 1.83 (2H,m), 2.43 (8H,m), 2.74 (2H,m), 3.43 (1H,m), 7.16 (3H,m), 7.35 (1H,m), 7.58 (1H,m), 8.73 (1H,br s); ^{13}C-nmr ($CDCl_3$) δ 19.1, 21.5, 23.0 (2), 34.1, 41.8, 44.7, 48.1, 52.1 (2), 69.2, 111.4, 118.3, 118.5, 119.2, 121.1, 122.2, 127.0, 136.7, 216.1; mass spec. (high res. elec. impact, m/Z). Found: 308.1917. Calcd for $C_{20}H_{24}N_2O$: 308.1889. From enamine **1a** and cyclohexenone was likewise prepared adduct **4a**: ir (KBr) 3410, 3260, 2945, 2855, 2800, 1715 cm^{-1};

^{1}H-nmr ($CDCl_3$) δ 1.63 (2H,m), 2.30 (7H,m), 2.75 (2H,m), 3.18 (1H,br s), 3.60 (4H,m), 6.83 (1H,d,J=2 Hz), 7.0-7.4 (3H,m), 7.55 (1H,m), 8.78 (1H,br s); ^{13}C-nmr ($CDCl_3$) δ 16.1, 25.4, 34.3, 39.8, 40.5, 46.0, 52.2 (2), 64.8, 67.0 (2), 111.4, 118.3, 118.9, 119.3, 120.9, 122.4, 126.2, 136.7, 217.2.

Wolff-Kishner Reduction of **4b** to **5**: A solution of 215 mg (0.70 mmol) of adduct **4b** in 3 ml of absolute ethanol was treated with 150 mg (4.68 mmol) of 90% hydrazine, and the mixture was heated to reflux for 1 h. The volatiles were removed under vacuum, and the residue was dissolved in 4 ml of diethylene glycol, this solution was charged with 275 mg (4.90 mmol) of potassium hydroxide, and was heated to 195°C for 4 h. The reaction mixture was cooled and poured into 25 ml of water, and this aqueous solution was extracted with a total of 100 ml of methylene chloride. The combined organic portions were dried (Na_2SO_4), and concentrated to give 240 mg of crude product, which was purified by preparative thin layer chromatography to yield 92 mg (45%) of compound **5** as a crystalline solid: mp 162-167°C ($CHCl_3$); ^{1}H-nmr ($CDCl_3$) δ 1.2 (1H,m), 1.62 (6H,m), 1.86 (2H,m), 2.3 (2H,m), 2.40 (4H,m), 3.16 (1H,br d,J=6 Hz), 7.0-7.4 (4H,m), 7.6 (1H,m), 8.05 (1H,br s); ^{13}C-nmr ($CDCl_3$) δ 19.7, 20.5, 23.1 (2), 25.4, 26.8, 29.2, 31.3, 42.2, 52.9 (2), 70.0, 111.1, 118.8, 119.0, 119.4, 120.7, 121.9, 127.3, 136.5.

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