The Contrasting Behavior of Cyclic and Acyclic 2-Amidomethyleneresorcinols towards Cyclization with Acetaldehyde

H. E. Zaugg, D. L. Arendsen and R. S. Egan

Department of Medicinal Chemistry, Abbott Laboratories, North Chicago, Illinois 60064

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The two cyclic amidomethylene resorcinols, **3a** and **3b**, readily undergo cyclization with acetaldehyde to the azacannabinoids **4** and **6**, respectively. However, the acyclic amidomethylene resorcinol **10**, under the same conditions, gives the benzodioxan **11**. This contrasting behavior is rationalized in terms of conformational differences between **3a,b** and **10**.

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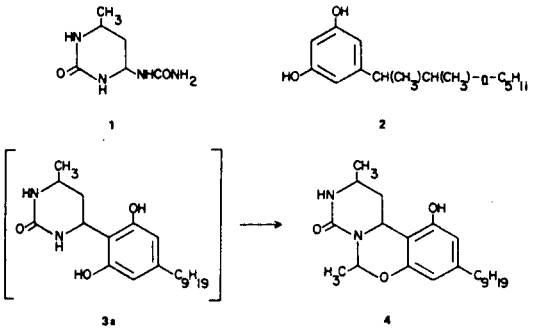
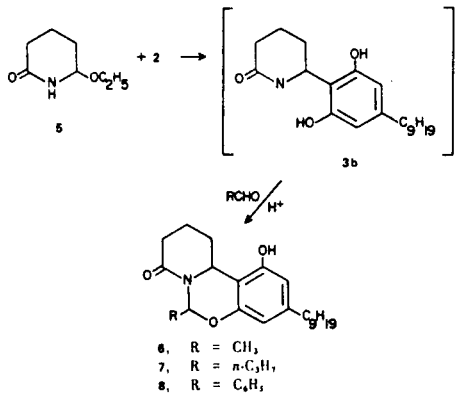
In connection with the synthesis of cannabinoid analogs, 5-(3-methyl-2-octyl)resorcinol **2** (1) was α-ureidoalkylated (2) by the pyrimidourea derivative **1**, readily prepared in turn from urea and acetaldehyde (3). Treatment of the amorphous condensation product **3**, thus obtained, with acetaldehyde under acid-catalyzed conditions (4) produced the diazacannabinoid **4**, isolable in crystalline form (after chromatography) despite the presence of 5 chiral centers.



Synthesis of the monoazacannabinoid **6** was likewise readily accomplished using the ethoxypiperidone **5** (5). Additional structural variation was introduced by utilizing *n*-butylraldehyde and benzaldehyde in the second step to produce compounds **7** and **8**, respectively. However, in agreement with the results of Zigeuner and Rauter (4), many attempts to condense intermediates of type **3** with acetone (and its derivatives, *e.g.*, isopropenyl methyl ether) were unsuccessful.



6, R = CH_3
7, R = n-C_3H_7
8, R = C_6H_5

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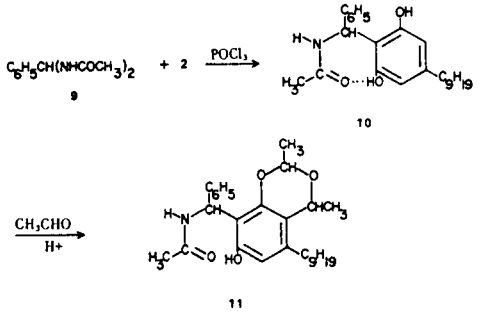
In an attempt to prepare a bicyclic analog of **6**, the resorcinol **2** was α-amidoalkylated with benzylidenebisacetamide (**9**) to give **10**. However, treatment of **10** with acetaldehyde under acid-catalyzed conditions did not lead to the target 1,3-benzoxazine. Instead, the only product isolated was the benzodioxan **11** formed as a result of aromatic substitution by the aldehyde. The structure of **11** was deduced primarily from its CMR spectrum (see Experimental).



The contrasting behavior of **3b** and **10** towards acetaldehyde can be rationalized in terms of conformational differences between them. The preferred (6) *syn* conformation of the acyclic amide provides for hydrogen bonding between carbonyl and hydroxyl groups, which in turn reduces rotation around the $(Ar)_2CH$-N bond (see structure **10**). The time-averaged proximity of NH to OH is thus reduced to the point where the aromatic substitution reaction can predominate over the cyclization leading to the desired 1,3-benzoxazine. Obviously in **3a,b**, constraints provided by the ring structure prevent hydrogen bonding between carbonyl and hydroxyl.

EXPERIMENTAL

All melting points were taken on a Thomas-Hoover melting point apparatus and are uncorrected. Ir spectra were obtained using a Perkin-Elmer Model 521 spectrophotometer. Pmr spectra were recorded using a Varian T-60 spectrometer. Chemical shifts are reported as δ relative to TMS (δ 0.0 ppm) using the following abbreviations: s = singlet; d = doublet; t = triplet; q = quartet, and m = multiplet. Thin-layer chromatograms (tlc) were carried out on Silic AR-7GF to distances of 10 to 15 cm. Spots were detected by visual examination under uv light, or by development with iodine vapor or arsenomolybdic acid spray.

CMR spectra were measured on an XL-100-15A/TT-100 spectrometer system in the pulse/Fourier transform mode. 8K data points were used. Off-resonance single frequency decoupling (ORSFD) experiments were used to assist in assignments. All spectra were of pyridine-d_5 solutions at ambient temperature. Approximately 250 mg. of each compound was used. Therefore, noise decoupled spectra required 2000 scans (27 minute acquisition time) and ORSFD spectra required 6000 scans (81 minutes). Chemical shifts are in ppm relative to tetramethylsilane. The mass spectra were recorded in an AEI Model MS902 mass spectrometer.

2,6-Dimethyl-11-hydroxy-9-(3-methyl-2-octyl)-1,2,3,12-tetrahydro-4*H*,6*H*-pyrimido[1,6-*c*][1,3]benzoxazine-4-one (**4**).

To a solution of 3.4 g. (0.0144 mole) of 5-(3-methyl-2-oxtyl)-resorcinol (**2**) (1) (65% *dl-erythro* and 35% *dl-threo*) in 20 ml. of anhydrous ethanol previously saturated with dry hydrogen chloride was added 3.7 g. (0.0216 mole) of the pyrimidylurea derivative **1** (3). After one hour of stirring at room temperature, tlc still showed the presence of unreacted **2** (R_f = 0.58; 10% methanol in chloroform). Another 3.7 g. portion of **1** was then added and stirring was continued at room temperature for another 60 hours. No **2** remained in the reaction mixture, so it was poured into cold water, extracted with chloroform, washed to neutrality with water and dried over anhydrous magnesium sulfate. Filtration and concentration to dryness in a rotary evaporator gave 5.2 g. of an amorphous powder, m.p. 95-105° which could not be crystallized, R_f = 0.43 (10% methanol in chloroform): ir (deuteriochloroform): 3600, 3440 (ν NH, OH), 3200 (broad, ν bonded OH), and 1670 cm^{-1} (ν C=O), consistent with structure **3a**.

A solution of 6.2 g. of this product in 125 ml. of acetaldehyde was treated with 1.2 ml. of 6*N* hydrochloric acid. The reaciton was complete in less than 30 minutes at reflux temperature (indicated by tlc using 10% methanol in chloroform). It was then poured into 1 l. of water containing an excess of sodium bicarbonate. Nitrogen was bubbled through the stirred suspension for 4 hours, and the yellow gum was taken up in chloroform (350 ml.), washed with water (2 x 300 ml.), and concentrated to dryness in a rotary evaporator. The residual brown glass (10.7 g.) was triturated with pentane (3 x 100 ml.), and the resulting friable solid was stirred vigorously for one hour each with two successive 100 ml. portions of pentane. Collection at the filter gave 6.85 g. of amorphous product, m.p. 115-130°. It was chromatographed on 180 g. of Florisil in a 100 x 2.5 cm column using 2 l. of 2% methanol in chloroform followed by 1 l. of 3% methanol in chloroform for elution. Five fractions were collected based on tlc using 5% methanol in chloroform. The first three (1.49 g.) were discarded. The other two were each treated with a few ml. of acetonitrile and allowed to stand for several days. The combined crystalline product from fractions 4 and 5 comprised 2.48 g., m.p. 180-193°, R_f = 0.19 (2% methanol in chloroform). One recrystallization from acetonitrile gave analytically pure **4**, m.p. 193-196°. Ir and Pmr spectra were both consistent with the assigned structure.

Anal. Calcd. for $C_{22}H_{34}N_2O_3$: C, 70.55; H, 9.15; N, 7.48. Found: C, 70.60; H, 9.19; N, 7.49.

11-Hydroxy-6-methyl-9-(3-methyl-2-octyl)-1,2,3,12-tetrahydro-4*H*,6*H*-pyrido[1,2-*c*][1,3]benzoxazine-4-one (**6**) and Analogs **7** and **8**.

A solution of 14.2 g. (0.06 mole) of the resorcinol **2** and 11.5 g. (0.08 mole) of 6-ethoxy-2-piperidone (**5**) (5,7) in 75 ml. of saturated ethanolic hydrogen chloride was stirred at room temperature for 24 hours. It was then worked up according to the foregoing procedure to give 26.3 g. of a glassy product (**3b**) which could be used in the next step, or purified by column-chromatography on Florisil using 2% methanol in chloroform for elution. (However, only 16.0 g. of still amorphous product was recoverable from the column.)

A solution of 7.4 g. (0.022 mole) of this crude resorcinol derivative in 40 ml. of acetaldehyde was treated with 1 ml. of 6*N* hydrochloric acid and stirred at room temperature for 2.5 hours. It was poured into water and worked up according to the foregoing procedure. However, in this case, the glassy product (6 g.) obtained from the chloroform extract partially crystallized (2.1 g., m.p. 227-229°) on treatment with acetonitrile. The remainder was chromatographed on Florisil (2% methanol in benzene) to give an additional 2.8 g., m.p. 229-230° (total yield: 4.9 g., 62%). Recrystallization from ethanol gave pure **6**, m.p. 230-232°; ir and pmr spectra were consistent with the assigned structure.

Anal. Calcd. for $C_{22}H_{33}NO_3$: C, 73.50; H, 9.25; N, 3.90. Found: C, 73,70; H, 9.55; N, 3.72.

By using *n*-butyraldehyde in place of acetaldehyde in the above procedure, there was obtained a 24% yield of 11-hydroxy-9-(3-methyl-2-octyl)-6-*n*-propyl-1,2,3,12-tetrahydro-4*H*,6*H*-pyrido-[1,2-*c*][1,3]benzoxazine-4-one (**7**), m.p. 205-206° (from acetonitrile); pmr (deuteriochloroform): was consistent with the assigned structure.

Anal. Calcd. for $C_{24}H_{37}NO_3$: C, 74.39; H, 9.63; N, 3.61. Found: C, 74.75; H, 9.85; N, 3.60.

Likewise, by replacing the acetaldehyde with benzaldehyde, there was obtained a 22% yield of 11-hydroxy-9-(3-methyl-2-octyl)-6-phenyl-1,2,3,12-tetrahydro-4*H*,6*H*-pyrido[1,2-*c*][1,3]-benzoxazine-4-one (**8**), m.p. 231-232° (from acetonitrile); pmr (DMSO-d_6) was consistent with the assigned structure.

Anal. Calcd. for $C_{27}H_{35}NO_3$: C, 76.94; H, 8.37; N, 3.32. Found: C, 76.56; H, 8.55; N, 3.20.

Attempts to substitute the following aldehydes, ketones or derivatives for acetaldehyde under a variety of conditions all failed: formaldehyde, formaldehyde diethyl acetal, chloroacetaldehyde diethyl acetal, pivalaldehyde, acetone, and methyl isopropenyl ether.

2-(α-Acetylaminobenzyl-5-(3-methyl-2-octyl)resorcinol (**10**).

A stirred solution-suspension of 11.8 g. (0.05 mole) of the resorcinol **2** (65% *dl-erythro* and 35%*dl-threo*) and 10.7 g. (0.052 mole) of benzylidenebisacetamide (**9**) (8) in 60 ml. of methylene chloride cooled to 2° in an ice bath was treated dropwise with 4.9 ml. (0.05 mole) of phosphorous oxychloride over a period of 5 to 10 minutes. Stirring was continued in the melting ice bath. A clear solution formed after 2 to 2.5 hours and precipitation of product began after 3 to 3.5 hours. After being stirred at room temperature overnight, the reaction mixture was treated with water (40 ml.) and more methylene chloride (70 ml.). After the slight exothermic reaction was complete, the organic layer containing suspended product was separated and washed successively with water (2 x 100 ml.), 5% sodium bicarbonate (100 ml.), and water (100 ml.). Filtration of the organic layer gave 5.00 g. of colorless crystalline powder, m.p. 204-208°. Concentration of the filtrate and cooling gave 2.58 g., m.p. 196-199°, as a second crop (7.58 g., 40% yield). Concentration to dryness left 10.8 g. of an amorphous glassy solid which could not be crystallized. Its pmr spectrum was similar to that of the crystalline fraction, suggesting it consisted of a mixture of stereoisomers. Recrystallization from acetonitrile of a sample of the 7.58 g. to constant m.p. gave pure **10**, m.p. 209-210° (probably

a single stereoisomer); ir (Nujol): 3400 (ν NH or OH), 3200 (broad, ν bonded OH), and 1610 cm^{-1} (ν C=O); pmr (DMSO-d_6): δ 9.0-9.8 (m, 2H, O*H*), 7.98 (d, 1H, J = 9 Hz, N*H*), 7.0-7.5 (m, 5H, C_6H_5), 6.64 (d, 1H, J = 9 Hz, Ar_2CHNH), 6.18 (s, 2H, C_6H_2) and 1.92 ppm (s, 3H, CH_3CO); m/e (M^+) 383.

Anal. Calcd. for $C_{24}H_{33}NO_3$: C, 75.16; H, 8.67; N, 3.65. Found: C, 74.85. H, 8.98; N, 3.59.

CMR Spectra of **2** and **10**.

Specific assignments of the aliphatic carbons in **2** were made by comparison with the known chemical shifts of the related hydrocarbon 3-methyloctane (9) and a knowledge of the effect of substitution of a phenyl ring for a proton down the length of the chain (10). Assignments could be made with only 2 carbons showing a deviation of more than 2 ppm from the calculated value. The aromatic carbon assignments for **2** could be made by considering the substituent effects on the chemical shifts of benzene (11). Reasonable agreement and unambiguous assignments were possible even though the effect of a methyl group was used for the entire C_9-side chain in the calculations. Nine of the carbon peaks in **2** (not all in the aliphatic side chain) were doubled (0.2 to 1.2 ppm) due to the mixture of *erythro* (65%) and *threo* (35%) isomers present. By elimination and by using the known chemical shifts for benzylamine (12), unambiguous assignments for the 20 different carbon atoms in **10** also could be made. However, the nine peaks that were doubled in **2** were not doubled in **10**, and shift comparisons clearly indicated that the aliphatic side chain in **10** has *erythro* stereochemistry. Furthermore, the doublet at 107.2 ppm corresponding to the two equivalent unsubstituted 4- and 6-carbon atoms in the *erythro* form of **2** remains a doublet at 107.6 ppm in **10**. However, the doublet at 101.5 ppm corresponding to the unsubstituted 2-carbon in **2** becomes a singlet at 114.1 ppm in **10** showing clearly that substitution of **2** has occurred between the two hydroxyl groups.

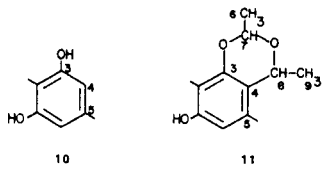
8-(α-Acetylaminobenzyl)-2,4-dimethyl-7-hydroxy-5-(3-methyl-2-octyl)-1,3-benzodioxan (**11**).

A stirred suspension of 2.0 g. of **10** in 50 ml. of acetaldehyde was treated with 0.5 ml. of 6 *N* hydrochloric acid. In less than 30 minutes the mixture became clear and shortly thereafter became cloudy again. After being stirred for 3 hours at room temperature, the starting material was completely consumed (tlc using 5% methanol in chloroform). The reaction mixture was then poured into water (300 ml.) containing an excess of sodium bicarbonate and a rapid stream of nitrogen was bubbled through the mixture for 2 hours. Water was decanted from the insoluble gum which was taken up in methylene chloride, washed with water, separated, filtered, and concentrated to dryness. Two 40 ml. portions of dry ether were added and successively removed by distillation, finally at 95° under vacuum (5-10 mm.) for 2 hours. The resulting colorless, amorphous solid (2.3 g.) was taken up in 10 ml. of hot acetonitrile and allowed to crystallize. There was obtained 0.93 g., m.p. 155-157°. Two more recrystallizations to constant m.p. gave pure **11**, m.p. 176-178° (probably a single stereoisomer: amorphous material obtained from the original filtrates had ir and pmr spectra very similar to those of the 176-178° material); ir (Nujol): 3400 (ν OH), 3100 (broad, ν bonded OH), 1630 (ν C=O), and 1515 cm^{-1} (secondary amide); ms: m/e (M^+) 453 (fragmentation pattern was consistent with the assigned structure).

Anal. Calcd. for $C_{28}H_{39}NO_4$: C, 74.14; H, 8.67; N, 3.09. Found: C, 73.88; H, 8.77; N, 3.07.

CMR Spectrum of **11**.

All but three of the 24 carbon atoms common to both **10** and **11** have chemical shifts within one ppm of each other. The three which do not are aromatic carbons and are numbered 3, 4, and 5 in the following partial structures.



10 11

In going from **10** to **11**, the chemical shift for the C-3 singlet decreases from 156.9 ppm to 150.6 ppm, that for C-4 goes from a doublet at 107.6 ppm to a singlet at 115.2 ppm and the C-5 singlet decreases from 147.4 to 144.1 ppm. Peaks for the four carbons present in **11** but not in **10** are at 21.1 ppm (q, 6- or 9-CH_3), 22.1 ppm (q, 9- or 6-CH_3), 68.8 ppm (d, 8-CH-), and 90.2 ppm (d, 7-CH-). These characteristics all fit the assigned structure for **11**.

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