The Aldehyde Analog of Indomethacin

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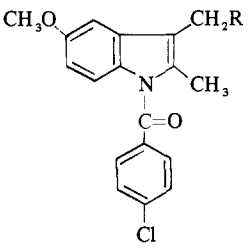
Indomethacin (**1**) is a potent, nonsteroidal antiinflammatory agent (indomethacin is 1-(*p*-chlorobenzoyl)-5-methoxy-2-methylindole-3-acetic acid).[1] As a drug,† it is widely prescribed for relief of rheumatic disorders. It was of interest, therefore, to synthesize the neutral analog of lower oxidation state, 1-(*p*-chlorobenzoyl)-5-methoxy-2-methylindole-3-acetaldehyde, and evaluate its activity *vis á vis* indomethacin.

Synthesis. The complete *N*-aroylindole ring system was constructed in one step[2] by Fischer condensation of N^1-(*p*-chlorobenzoyl)-*p*-methoxyphenylhydrazine hydrochloride with 3-acetyl-1-propanol. The resulting indolyl-3-ethanol



1, R = CO_2H
2, R = CH_2OH
3, R = $CH(OH)SO_3^-Na^+$
4, R = CH=O

intermediate **2** was oxidized to crude aldehyde in anhydrous dimethyl sulfoxide containing dicyclohexylcarbodiimide and a catalytic amount of phosphoric acid. This method [3] for oxidizing a primary alcohol to aldehyde was preferred because of its selectivity and the mildness of the conditions. These considerations are important because the related indole-3-acetaldehyde is reported to be a relatively unstable species, decomposing readily in acidic or basic media.[4] N-Deacylation also occurs under similar conditions.[2,5] The aldehyde was purified by forming the bisulfite adduct **3** which was later cleaved in a two-phase HCl–benzene system to afford pure indomethacin aldehyde (**4**). Recrystallization from *tert*-BuOH afforded pure indomethacin aldehyde (**4**), mp 121.5–123°, in the form of pale yellow needles.

Biological Activity. The antiinflammatory activity of indomethacin and the aldehyde **4** was compared concurrently in the carrageenan-induced foot edema test in the rat.[6] The aldehyde was found to be 0.6–0.7 as active when administered in solution (0.1 ml of DMA and 0.4 ml of emulphor diluted with 20 ml of water); however, it was considerably less effective when in suspension (homogenized in 1% methanol). In contrast, indomethacin's potency was about the same whether given in solution or in suspension.

The aldehyde **4** was found to undergo oxidation *in vivo* to indomethacin. This is shown in Table I by measuring the indomethacin level in the blood plasma of rats given an oral dose of aldehyde in DMA suspension. The plasma levels obtained[7] for the same dose of indomethacin itself are included in Table I for comparison. The aldehyde could be detected qualitatively in the plasma for up to 2 hr after administration.

†The registered trademark of Merck & Co., Inc., is INDOCIN.

Table I.[a] Plasma Levels (μg/ml) of Indomethacin

Time, hr	Compound administered: Indomethacin aldehyde	Compound administered: Indomethacin[b]
0.5	10.3	45.2
1	11.7	40.6
2	11.6	37.5
4	20.8	25.7
6	12.8	21.1
8	11.3	20.4

[a]The animals received 10 mg/kg, po, of each drug. The values for the aldehyde represent the average of three rates per test given an oral dose in DMA suspension. The testing procedure was described previously.[7] The data for iodomethacin were taken from Table 3 in ref 7. [b]See ref 7.

Experimental Section‡

1-(*p*-Chlorobenzoyl)-5-methoxy-2-methylindole-3-ethanol (2). A stirred mixture of N^1-(*p*-chlorobenzoyl)-*p*-methoxyphenylhydrazine hydrochloride[8] (98.0 g, 0.314 mol), MeOH (540 ml), and 3-acetyl-1-propanol (from Aldrich Chemical Co., Milwaukee, Wis.) (32.1 g, 0.314 mol) was refluxed under N_2 for 3 hr. The solvent was then removed, and the residue partitioned between $CHCl_3$ (500 ml) and H_2O (500 ml). The aqueous layer was separated and reextracted twice with 100 ml of $CHCl_3$. The combined $CHCl_3$ extracts were charcoaled and the solvent was removed to afford 107 g of crude **2**. Three crystallizations from EtOAc (1 ml/g) gave 54.3 g (50.2%) of pure alcohol: mp 121–123°; λ_{max}^{MeOH} 231 mμ (ε 20,420), 263 (15,540), 320 (6390). *Anal.* ($C_{19}H_{18}ClNO_3$) C, H, N, Cl.

1-(*p*-Chlorobenzoyl)-5-methoxy-2-methylindole-3-acetaldehyde (4). To a well-stirred solution of **2** (78.5 g, 0.228 mol) and solid (99%) phosphoric acid (from Gallard-Schlessinger Chemical Mfg. Corp., Carle Place, N. Y.) (13.5 g) in dry DMSO (215 ml) was added dicyclohexylcarbodiimide (141 g, 0.70 mol) over a 5-min period. The oxidation was extremely exothermic so that when the reaction temperature began to rise, the flask was immediately immersed in ice–MeOH cooling bath. When the exotherm subsided, the cooling bath was removed and the orange mixture stirred at 25° for 2 hr. It was then filtered and the cake (dicylcohexylurea) washed free of color with four 250-ml portions of CH_2Cl_2. The organic phases were combined, washed until neutral with four 1-l. portions of H_2O, charcoaled, and dried, and the solvent was removed *in vacuo* to afford crude **4** as a foam (119 g). The ir ($CHCl_3$) showed strong aldehydic C–O at 5.79 μ, but tlc revealed a complex mixture. This material was purified *via* the bisulfite adduct **3** as follows.

A mixture of crude aldehyde (112 g, foam) and EtOH (65 ml) was heated to 60° and then allowed to cool to 30° with vigorous stirring to effect homogenization. To this thick fluid was added a saturated aqueous $NaHSO_3$ solution (400 ml) over a 5-min period. Bisulfite adduct formation was rapid and the yellow product separated voluminously. After 1 hr of stirring, the solids were filtered (coarse funnel), washed with two 200-ml portions of EtOH, similarly with ether, and dried to yield 118.5 g (contaminated with $NaHSO_3$). An analytical sample (dried at 80°) of **3** was obtained by crystallization from boiling H_2O (7 ml/g), mp 160–161° dec. *Anal.* ($C_{19}H_{17}ClNO_6SNa$) C, H, N, S.

The crude adduct was cleaved to **4** as follows. 60 g was added to C_6H_6 (500 ml) and H_2O (500 ml), and the stirred mixture was warmed to 35°. Concentrated HCl (15 ml) was then added slowly to control foaming due to gas evolution. When the addition was complete, the mixture was heated on the steam bath for 1 hr and then cooled to 25°. The resulting emulsified mixture was filtered through a mat of supercel. The C_6H_6 phase of the filtrate was separated, washed repeatedly with H_2O until neutral, charcoaled, dried, and concentrated to afford 10.5 g of crystalline **4**. The wet supercel cake, containing some unreacted **3**, was recycled as above to provide an additional 3.65 g. The combined crops (14.1 g) were recrystallized twice using 5 ml/g of 90% *tert*-BuOH–10% EtOH to afford 8.0 g of pure aldehyde (18% yield from **2**) as yellow needles:

‡Melting points were determined with a Thomas-Hoover Uni-melt apparatus in unsealed capillary tubes and are uncorrected. We are indebted to Mr. A. Kalowsky for ultraviolet spectra and to Mr. R. N. Boos and his staff for microanalyses. Where analyses are indicated only by sumbols of the elements, analytical results for those elements were within ±0.4% of the theoretical values. Solvents were removed on a rotary evaporator after drying with $MgSO_4$.

mp 121.5–123.0°; λ_{max}^{MeOH} 232 mμ (ε 20,440), 263 (15,930), 320 (6360). *Anal.* ($C_{19}H_{16}ClNO_3$) C, H, N, Cl.

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Inhibition of Catecholamine Uptake by Conformationally Restricted Phenethylamine Derivatives

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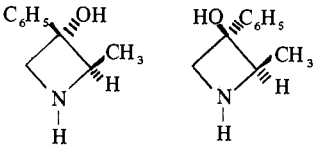
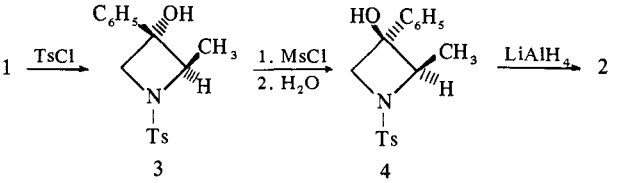
Norepinephrine uptake inhibition is one of the important means by which drugs can affect the adrenergic nervous system. Several studies have appeared on the structural requirements for the inhibition of catecholamine uptake.[1-4] The work on this subject has been reviewed.[5] Previous investigations on the structural requirements of adrenergic drugs have utilized conformationally restricted analogs of phenethanolamine.[6-8]

In an attempt to gain further insight into the stereochemical requirements for the inhibition of catecholamine uptake, we have prepared some azetidine analogs of ephedrine. In this study *trans*-3-phenyl-2-methylazetidin-3-ol (**1**) and *cis*-3-phenyl-2-methylazetidin-3-ol (**2**)† may be considered cyclized ephedrine analogs with a minimum deletion in the number of atoms accompanying the structural change. The azetidines **1** and **2** may be con-



1 **2**

sidered analogous to the threo and erythro configurations of ephedrine, respectively. Hortmann and Robertson[9] have recently reported the synthesis of **1** and an epimeric mixture of **1** and **2**. We would like to report the synthesis of pure **2** utilizing **1** as the starting material. The azetidine **1** was treated with TsCl to give the sulfonamide **3** which in turn was converted to the epimeric sulfonamide **4** by allowing **3** to react first with $MeSO_2Cl$ and then H_2O. The nmr spectrum of **3** showing a shielded methyl doublet at δ 0.87 (J = 6.5 Hz) was consistent with the cis disposition of the methyl group with the phenyl ring, while by comparison the sulfonamide **4** showed a methyl doublet at δ 1.40 (J = 6.5 Hz).[9-11] The sulfonamide **4** was reduced with $LiAlH_4$

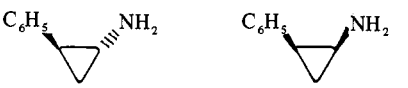


3 **4**

giving the desired **2**[12] and as expected in the nmr spectrum **2** showed a methyl doublet at a lower field δ 1.31 (J = 6.5 Hz) than that observed for **1**, δ 0.74 (J = 6.5 Hz).

Biological Results. The ability of racemic **1** and **2** as well as the desmethylazetidine analog, 3-phenylazetidin-3-ol (**5**),[9] to inhibit (−)-H^3-norephinephrine uptake in rat vas deferens is shown in Table I. Indications are that the stereochemistry of the α-methyl group relative to the phenyl or hydroxyl groups in the azetidine series plays a significant role in the compounds' ability to prevent uptake of (−)-norepinephrine with the relative order of activity being **1** > **2** = **5** in a ratio of 7:1:1.‡

Similarly, *trans*-2-phenylcyclopropylamine (**6**) and *cis*-2-phenylcyclopropylamine (**7**) were investigated for their ability to prevent the uptake of (−)-H^3-norepinephrine in



6 **7**

rat vas deferens as shown in Table I. It is assumed that these compounds are competitive inhibitors of norepinephrine uptake. Using these two conformationally restricted molecules **6** and **7** should provide a better understanding of what the stereochemical relationship should be between the amino and phenyl functions in phenethylamine molecules for the prevention of norepinephrine uptake in the peripheral nervous system. A marked stereospecificity can be seen between the isomers where the trans isomer **6** is greater than 600 times the cis isomer **7** in inhibiting (−)-H^3-norephinephrine uptake in the rat vas deferens. This is quite similar to differences observed by Horn and Snyder[4] for **6** and **7** in blocking norepinephrine uptake in the rat hypothalmus. This seems to indicate that the anticlinical conformation is the preferred conformation for phenethylamine-type drugs in norepinephrine uptake inhibition in both peripheral and central nervous systems.

Experimental Section

Melting points (uncorrected) were determined on a Thomas-Hoover melting point apparatus. Spectral data were obtained using Perkin-Elmer 237 and Varian A-60A spectrometers. Analyses were performed by Clark Microanalytical Laboratory, Urbana, Ill. Analytical results for elements indicated were within ±0.4% of the theoretical values.

Pharmacologic Testing. For the results described in Table I albino rats weighing 305–395 g were killed and both vasa deferentia were isolated. Tissues were transferred to an oxygenated 5-ml Kreb's solution at 37.5°. The tissue monoamine oxidase which degrades norepinephrine was inhibited by exposing the tissue to 10^{-4} M iproniazid for 30 min. The iproniazid-inhibited tissues were transferred to two beakers each containing 5 ml of the Kreb's solution. Thus, one tissue served as a control and the contralateral tissue served as experimental. Both tissues were incubated with (−)-H^3-

†Cis and trans refer to the relationship between the C-2 CH_3 and the C-3 OH; thus, **1** has CH_3 trans to OH and **2** has CH_3 cis to OH. All materials are racemic although only a single isomer is drawn.

‡As compared to the effects produced by **2**, the contraction of the isolated vas deferens to (−)-norepinephrine (10^{-6} M) was potentiated more by 10^{-5} M (3-min incubation) of **1**.