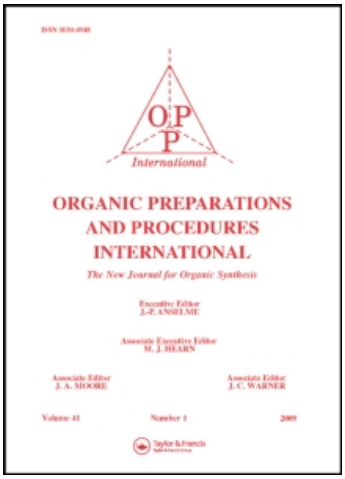


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# PRACTICAL SYNTHESIS AND CHARACTERIZATION OF 7-BENZYLIDENENALTREXONE (BNTX)

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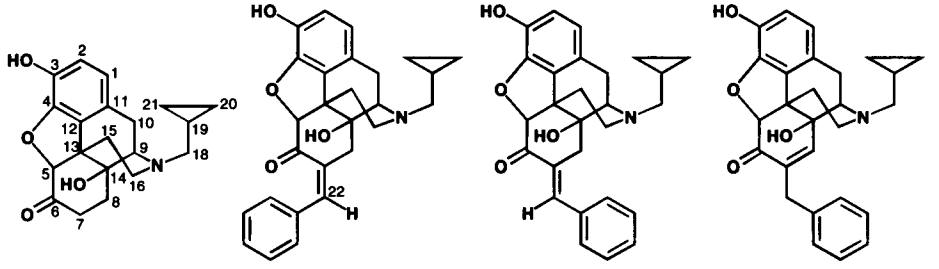
Investigations of the δ-opioid receptor have been greatly aided by the recent development of potent nonpeptide δ-opioid antagonists.[1] In particular 7-benzylidenenaltrexone (BNTX) had been characterized as a highly selective $\delta_1$-opioid receptor antagonist[2] useful in probing δ-receptor subtypes.[3] Since attempts to scale-up the published procedure[1,4] gave poor yields, alternative synthetic approaches were investigated. An improved synthetic pathway, useful for the preparation of gram amounts of BNTX, is described along with full characterization of this important $\delta_1$-selective ligand as *anti*-7-benzylidenenaltrexone (**3**).

On a 1 g scale, the aldol condensation of naltrexone (**1**) with excess benzaldehyde in methanolic sodium hydroxide following the literature report,[4] gave essentially the reported yields, although a modification of the work-up conditions was required. Thus, in our hands, basification to pH 10, before extraction of the acidified reaction mixture with chloroform, was required to allow



**1** **2** **3** **4**

BNTX to be extracted along with unreacted naltrexone. Unfortunately attempts to carry out this reaction starting with 2-5 g of naltrexone (**1**) resulted in diminishing yields of highly impure BNTX.

Aldol condensations of aromatic aldehydes using catalysis by strong bases, strong acids,[5,6] Lewis acids,[7-9] or acid-base combinations[10,11] have been reported. In our hands benzaldehyde failed to react with naltrexone using lithium iodide[8] or titanium tetrachloride[9] catalysts, although a model reaction of benzaldehyde with 2-methoxycyclohexanone did take place. Attempted aldol condensation of benzaldehyde with naltrexone under acidic conditions[5] afforded intractable gums containing very little

product. Since these results mirrored those reported for the attempted preparation of didehydroparadols by the aldol condensation of vanillin with alkyl methyl ketones,[10] we were encouraged to try the soft acid/soft base conditions which gave good results in the didehydroparadol synthesis.

Treatment of an equimolar mixture of naltrexone (**1**) and benzaldehyde in benzene-ether with a two fold excess of equimolar pyrrolidine and acetic acid gave, after 48 hours, 80% yield of 94% pure BNTX. The work-up consisted of acidification of the reaction mixture with hydrochloric acid, which led to precipitation of BNTX hydrochloride, washing of the aqueous acidic layer with ether and basification of both the aqueous phase and the precipitated solid to pH 10. Extraction afforded BNTX base. Work-up omitting the acidification step gave lower yields of BNTX as did the work-up conditions reported for the base catalyzed condensation.[1] Omitting the ether co-solvent had a slightly beneficial effect on the reaction yield (87%) and use of toluene in place of benzene gave an 82% yield of BNTX of comparable purity to that obtained in the benzene reaction. The yield in a reaction starting with 5 g of naltrexone (**1**) was comparable to that of the 1 g reaction (87% of BNTX•HCl), suggesting that these reaction conditions are suitable for scale-up.



Although two isomers of BNTX have been described,[1] the data are insufficient to unambiguously distinguish the three possible structures which could be associated with the aldol condensation product of benzaldehyde and naltrexone, *i. e. syn-* and *anti*-7-benzylidenenaltrexone (**2** and **3**, respectively) and 7-benzyl-7,8-dehydronaltrexone (**4**). Specifically, the observation of a singlet vinyl resonance in the $^1$H NMR spectrum[1] is expected for all three structures and isomerization[1] between the three structures is not unexpected. Similarly, all three will provide the reduction product 7-benzylnaltrexone.[1] Consequently we decided to undertake a thorough structure determination. With the aid of COSY, DEPT and HETCOR spectra, the proton and carbon chemical shifts were unambiguously assigned (see Experimental Section). The observed homonuclear NOESY interaction between the aromatic benzylidene hydrogens (7.51 ppm) and the C-8 methylene hydrogens (2.45 and 3.15 ppm) was consistent with either structure **3** or **4**, but not with structure **2**. This conclusion was also consistent with the absence of any NOE interaction between the single proton at 7.61 ppm, identified as the vinyl hydrogen by its NOE interaction with the aromatic benzylidene hydrogens (7.51 ppm), and the hydrogens at C-8. The UV data served to distinguish structures **3** from **4**: the compound isolated from the reaction mixture is a yellow solid with $\lambda_{max}$ 303 nm (MeOH, $\varepsilon$ 14,400), indicating that the phenyl group is conjugated with the $\alpha,\beta$-unsaturated ketone and confirming that the structure is **3**, *anti*-7-benzylidenenaltrexone.

The stability of aqueous and ethanolic solutions of BNTX•HCl at room temperature was monitored by HPLC using naltrexone hydrochloride as internal standard. At a BNTX•HCl concentration of $10^{-3}$ M aqueous solutions were reasonably stable for 1 week; ethanolic solutions, at the same concentration, exhibited some decomposition after three days. After 35 days in ethanol solution the area of the BNTX peak had decreased to 75% of its original value and a new, somewhat faster eluting peak was observed. The same general situation obtained in water, but the area of the BNTX peak had decreased by approximately 10%. The faster eluting peak appears to be the *syn*-isomer **2**.

In summary, we have developed an improved synthesis for the important $\delta_1$-opioid selective antagonist BNTX•HCl which affords the product in consistently high yield (>75%) and purity (>90%) and which is amenable to scale-up without compromising either the yield or the purity. The structure was confirmed to be *anti*-7-benzylidenenaltrexone (**2**) as proposed by Portoghese.[1]

## EXPERIMENTAL SECTION

Melting points were determined on a Thomas Hoover capillary apparatus. Optical rotations were determined at the sodium D line using a Rudolph Research Autopol III polarimeter (1 dm cell). NMR spectra were recorded on a Bruker AM-500 spectrometer using tetramethylsilane as internal standard. High performance liquid chromatography (HPLC) analyses were carried out using a Rainin dual pump Macintosh controlled system equipped with a variable wavelength UV detector (Knauer). UV spectra were recorded on a Varian 2290 spectrophotometer. Naltrexone was provided by the National Institute on Drug Abuse (NIDA).

***anti*-7-Benzylidenenaltrexone Hydrochloride (3).**- Glacial AcOH (1.68 mL, 0.0293 mol) was added slowly to pyrrolidine (2.45 mL, 0.0294 mol) at 0°C under argon. After stirring for 1 h a white solid usually formed. The mixture was allowed to warm to room temperature and toluene (80 mL) was added, followed by naltrexone (**1**) (5.01 g, 0.0147 mol). A solution of benzaldehyde (2.98 mL, 0.0293 mol) in toluene (10 mL) was added dropwise, the flask was sealed under argon and kept at room temperature for 4 days. The color of the solution changed from pale yellow to dark brown during that time. Addition of 1N HCl (500 mL) led to precipitation of a light orange solid which, by HPLC analysis [$C_{18}$ μ bondapak, $CH_3OH$:$H_2O$:$(NH_4)_2CO_3$ 80:20:0.35), 1.5 mL/min, 254 nm] is 99.6% pure BNTX•HCl. The separated aqueous phase and the precipitated solid were washed with $Et_2O$ (4 x 100 mL), basified with conc. $NH_4OH$ to pH 10 and extracted with $Et_2O$ (4 x 200 mL). The combined extract was dried over anhydrous $Na_2SO_4$ and concentrated to afford 6.07 g (96.6% yield) of BNTX which, by HPLC analysis, was 96% pure. Treatment of this solid with $Et_2O$ (600 mL) left an undissolved brown gum (0.26 g) which was removed by decantation. The solution was acidified with 10% HCl in MeOH (20 mL) under argon and the resulting salt was collected by filtration (5.95 g, 78% overall yield). This solid exhibits a single spot, $R_f$ 0.76 on $SiO_2$ (Whatman) TLC ($CHCl_3$:$CH_3OH$:conc. $NH_4OH$ 80:18:2) and is 98% pure by HPLC with $\lambda_{max}$ 303 ($CH_3OH$, 14,400); [α]= -33.1 (c 1.03, $CH_3OH$), $^1H$ NMR (500 MHz, DMSO-$d_6$): δ 0.41 (m, 1, H-20); 0.51 (m, 1, H-21); 0.58 (m, 1, H-21); 0.68 (m, 1, H-20); 1.09 (m, 1, H-19); 1.67 (d, $J_{gem}$ = 13.1 Hz, 1, H-15a or H-15e); 2.45 (dd, $J_{gem}$ = 16.9 Hz, $J_{8,22}$ = 3.0 Hz, 1, H-8a or H-8e); 2.38 (dt, $J_{gem}$ = 13.1 Hz, $J_{15,16}$ = 4.5 Hz, 1, H-15a or H-15e); 2.71 (m, 1, H-16a or H-16e); 2.91 (m, 1, H-18a or H-18e); 3.09 (d, $J_{gem}$ = 9.8 Hz, 1, H-16a or H-16e); 3.15 (d, $J_{gem}$ = 16.9 Hz, 1, H-8a or H-8e); 3.25 (dd, $J_{gem}$ = 18.9 Hz, $J_{9,10}$ = 6.6 Hz, 1, H-10a or H-10e); 3.41 (overlapping with $H_2O$ signal, m, H-10a or H-10e and H-18a or H-18e); 4.08 (d, $J_{9,10}$ = 6.4 Hz, 1, H-9); 6.70 (d, $J_{1,2}$ = 8.11 Hz, 1, H-1 or H-2); 6.79 (d, $J_{1,2}$ = 8.11 Hz, 1, H-1 or H-2); 7.43 (m, 3, m- and p-ArH); 7.51 (m, 2, o-ArH); 7.61 (d, $J_{8,22}$ = 2.6 Hz, 1, H-22). $^{13}C$ NMR (500 MHz, DMSO-$d_6$): δ (most quaternary carbons are unassigned): 2.6 (20 or 21), 5.3 (20 or 21), 5.7 (19), 23.4 (10), 23.8 (13), 28.4 (15), 33.9 (8), 45.5 (16), 56.9 (18), 60.1 (9), 69.4 (14), 87.4 (5), 118.3 (1 or 2),

120.3 (1 or 2), 121.4, 128.4, 128.6 (Ph), 129.5 (Ph), 130.3, 130.7 (Ph), 134.5, 139.7, 140.7 (22), 143.9, 185.7 (6). The material decomposes above 200°C prior to melting.

*Anal.* Calcd. for $C_{27}H_{27}NO_4 \cdot 1.1\ HCl \cdot 1.5\ H_2O$: C 65.20; H 6.27; N 2.82; Cl 7.86

Found: C 65.32; H 6.45; N 3.04; Cl 7.81

**Stability of Aqueous and Ethanolic Solutions of *anti*-7-Benzylidenenaltrexone Hydrochloride (2).**- Solutions containing 9 x $10^{-4}$ M BNTX (**3**) hydrochloride and a similar concentration of naltrexone (**1**) hydrochloride in distilled $H_2O$ and in absolute EtOH were monitored over a 36 day period. Three aliquots of each solution were analyzed daily (in triplicate) by HPLC and TLC. The HPLC analysis was carried out on a $C_{18}$ μ bondapak cartridge, eluting with MeOH:$H_2O$:$(NH_4)_2CO_3$ 80:20:0.35 at a flow rate of 1.5 mL/min and monitoring at 254 nm. The retention times of naltrexone and BNTX, under these conditions, were 6.9 min and 9.9 min, respectively. TLC analysis was performed on $SiO_2$ plates, eluting with $CHCl_3$:MeOH:$NH_4OH$ 80:18:2. The faster eluting material appears to be the *syn* isomer **2**.

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