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SYNTHESIS OF 2-AMINOMORPHINE AND 2-AMINOCODEINE. REDUCTION OF AROMATIC NITRO GROUPS WITH FORMAMIDINESULFINIC ACID.

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Our interest in the stereoselective reduction[2] of the carbonyl groups of various oxymorphone derivatives with formamidinesulfinic acid (FSA) led to a result indicating that dihydrocodeinone[3] underwent ring-oxygen scission[4] under the conditions of reduction with this reagent. This observation[4] has prompted interest and speculation as to the scope and mechanism of this reaction by others [5], as well as ourselves.

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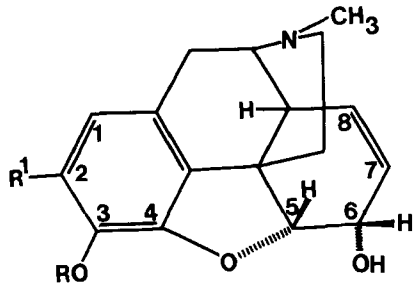
During the course of our synthetic work on morphine and codeine compounds (and derivatives affecting the central nervous system), the need arose for a facile method of reduction of the 2-nitro derivatives to the corresponding amines of morphine and codeine. An extensive search of the literature[6-8], revealed two methods: one was a tin and hydrochloric acid reduction of 2-nitromorphine (1a) to 2-aminomorphine (1c), by Bognar and Gaal[6]. The other was an electrolytic reduction of 2-nitrocodeine (1b), to 2-aminocodeine (1d) by Ochiai and Nakamura[7]. Since these experimental methods were somewhat laborious and in view of the limited quantities of starting materials available to us, we wanted to avoid these acidic reaction conditions and so chose to explore the reduction of the aromatic nitro group by FSA in an alkaline medium.

The 3-phenolic-6-oxo-dihydromorphine derivatives reduced with FSA so far[2-5], have shown no ring -oxygen scission[4] (as in the reduction of dihydrocodeinone); therefore we were all the more curious as to the outcome of FSA reduction of the nitro group on morphine and particularly on codeine. Though FSA has been briefly mentioned as a reducing agent[9], for the aromatic nitro group, inter alia[10], no published experimental procedure using this agent was found for the preparation of aromatic amines.

We now report the facile reduction of 1a and 1b to the corresponding amino derivatives 1c and 1d in yields of 60 and 81% respectively.



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a, R=H; $R^1=NO_2$
b, $R=CH_3$; $R^1=NO_2$
c, R=H; $R^1=NH_2$
d, $R=CH_3$; $R^1=NH_2$

The reduction of 1b to 1d deserves further comment. The product obtained by us is a known compound, described by earlier workers; Bognar and Gaal have reported this compound to be air and moisture sensitive. We obtained a homogeneous product that was further purified by preparative chromatography on silica gel plates for purposes of spectral characterization. This sample melted at 85°C (lit.[6] 83°C); its mass spectrum showed an exact molecular weight at 314.1638 amu (theoretical weight,

314.1631). The IR spectrum showed an absence of bands at 1527 and 1338 cm^{-1} which were characteristic of the nitro group of 1b. The ^1H -NMR spectrum of 1d was of particular interest toward further assurance of the intact oxygen bridge and thus the identity of the product as 2-aminocodeine; it showed a broad singlet at δ 6.02 due to the aromatic proton at C-1; the vinylic protons at C-7 and C-8 appeared as a set of doublets (J = 10 Hz) at 5.73 and 5.28 respectively. The 5β-proton appeared as a doublet at 4.84 (J = 6 Hz). The 6α-hydroxy orientation was confirmed by observation of the 6β-proton which appeared as a broad multiplet centered at 4.16. These chemical shift values and coupling constants are in harmony with those in the literature[11-16]. These considerations show that 1b is reduced smoothly to 1d with no obvious side reaction. It must also be noted here that although this reaction was carried out under homogeneous conditions (using ethanol as cosolvent) the opening of the 4, 5α-ether bridge did not occur in this reduction as was the case in the reduction of 6-oxo compounds in the codeine series, reported by Brine and coworkers[5].

The ^1H -NMR spectrum of 2-aminomorphine (1c) in dimethylsulfoxide (d_6) showed a broad singlet at 5.84 due to the aromatic proton at C-1; a set of doublets (J = 10 Hz) at 5.50 and 5.21 attributable to the protons at C-7 and C-8 respectively, a doublet at 4.64 (J = 6 Hz)

due to the 5β-proton and a broad multiplet centered at 4.06 assignable to the 6β-proton. The N-methyl singlet appeared at 2.30.

In an effort to elucidate the general synthetic utility of this reagent for the preparation of aromatic amines by reduction of the corresponding nitro groups in common organic compounds, we applied this methodology to 2-nitrobenzoic acid (2), 3-nitrophenol (3), and 4-nitrotoluene (4); the sole products obtained were 2-aminobenzoic acid (5), 3-aminophenol (6), and 4-aminotoluene hydrochloride (7) in isolated yields of 85, 90, and 56% respectively. Though no efforts were made to optimize these yields, these results nevertheless indicate the preparative potential of FSA as a reducing agent for aromatic nitro groups.

This method may also be considered as an attractive chemical mode for compounds that are acid sensitive. It is also clear that FSA has now been demonstrated to be valuable for modification of the aromatic moiety (ring A) of morphine derivatives , in addition to ring C of related substances[2-5].

Experimental Section.

General experimental procedures were as reported earlier[2,4]. Melting points were obtained on a thermolyne melting point apparatus, model No. MP-1200, and are

reported uncorrected. Thin layer chromatography was performed on silica gel plates obtained from Analtech Inc., Newark,Delaware. Solvent system was EtOAc:MeOH: NH_4OH, 75:20:5 by volume. Aromatic nitro compounds were obtained from Aldrich Chemical Co., Inc., Milwaukee, Wisconsin. ^{1}H-NMR spectra were obtained on a Varian XL-100 spectrometer and are reported in ppm (δ) relative to tetramethylsilane (TMS) as internal standard. Mass spectra were determined on a Dupont 21-492 double focussing instrument equipped with electron impact source and direct sample introduction probe. FSA was obtained from Eastman Organic Chemicals, Rochester, N.Y. Elemental analyses were performed by Spang Microanalytical Laboratory, Eagle Harbor, Michigan.

2-Aminomorphine (1c). To 1.77 g (0.005 mol) of 1a hydrochloride[6,17] in H_2O (35 ml) was added NaOH (1.87 g, 0.047 mol) in H_2O (20 ml). This mixture was maintained under a stream of N_2 gas and stirred magnetically. To the resulting blood-red solution was added FSA (2.25 g, 0.02 mol) and the reaction mixture was maintained at 90-100°C on a water bath.Within 15 min the color was discharged; heating was continued for 1 hr. During this period an off-white precipitate appeared. The reaction was stopped and the mixture was chilled in ice. The pH of the supernatant was 9.8 (this was the optimum

pH at which the free base 1c precipitated from the aqueous mixture). Filtration gave 950 mg of crude 1c, (60%). Recrystallization from MeOH-H_2O gave needles[10] which softened at 156°C and decomposed at 260°(lit.[6] 256°C. Mass spectrum m/e 300 (M^+,100%). IR (KBr) 3450, 3350 cm^{-1} (NH_2); broad band 3200 (OH). Treatment of an ethanolic solution of 1c (R_f= 0.21) with ethereal diazomethane converted it to 1d (R_f= 0.41). An analytical sample was obtained by recrystallizations from absolute EtOH; this sample decomposed at 258°C (lit.[17] 258°C). Anal. Calcd for $C_{17}H_{20}N_2O_3$: C, 67.96; H, 6.71; N, 9.32. Found: C, 68.05; H, 6.82; N, 9.22.

2-Aminocodeine (1d). The free base 1a was converted to its methyl ether 1b by treatment with an ethereal solution of diazomethane following the procedure of Ochiai and Nakamura[7]; 2 g (0.006 mol) of 1b obtained thus was dissolved in EtOH (30 ml) and H_2O (10 ml). A solution of NaOH (1.44 g, 0.036 mol) in H_2O (20 ml). was made up and 10 ml of this was added to the solution of 1b; to the remaining 10 ml of NaOH was added 1.94 g (0.024 mol) of FSA and this was added to the alkaline solution of 1b. The reaction mixture was heated with stirring on a water bath at 90° under N_2 for 1.5 hr. During this period the orange color of the mixture was discharged. Upon evaporation of EtOH, the aqueous residue was extr-

acted with $CHCl_3$; the organic layer was washed with H_2O, dried (Na_2SO_4) and flash evaporated. The residue upon addition of $CHCl_3$-petroleum ether (60-90°) gave off-white crystals (1.4 g, 81%). This material, although homogeneous upon TLC (R_f= 0.41) appeared to be sensitive to air and moisture[6], and hence was maintained under N_2, A pure sample of the free base was obtained by preparative chromatography on 1000 micron silica gel plates. The sample so obtained melted at 85°C (lit.[6] mp 83°C). IR (KBr) 3450, 3350 cm^{-1}(NH_2), 3200 (broad, OH); mass spectrum m/e 314 (M^+, 100%); ^{1}H-NMR ($CDCl_3$) 3.92 (s, 3H, OCH_3), 2.42 (s, 3H, NCH_3). A portion of this substance was converted into 2-bromocodeine following the procedure of Ochiai and Nakamura. This derivative melted at 161-163°C (lit.[7] mp 160-161°C); mass spectrum m/e 377 (M^+).

General procedure for obtaining compounds 5, 6, and 7.

The acidic nitro compounds were dissolved in aqueous alkali and treated with a four molar excess of FSA following conditions as in the preparation of 1c. The products were isolated by reducing the pH to the appropriate isoelectric point, followed by filtration or extraction with ether. Compound 4 was dissolved in aqueous EtOH and treated with FSA and NaOH[19] as in the preparation of 1d.

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17. H. Wieland and P. Kappelmeier, Justus Liebig's Ann., 382, 306 (1911); these authors formulated the compound as 2-nitrosomorphine; it was subsequently identified as 2-nitromorphine by Ochiai and Nakamura[7].

18. This substance crystallized with one molecule of water as evidenced by elemental analysis; the analysis reported by Weiland and Kappelmeier also was for a monohydrate of the free base 1c[17].

19. A two molar excess of NaOH over FSA was found to be satisfactory in all these reductions of the nitro compounds.

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