毎月1回25日発行 37巻2号 平成元年2月25日発行 昭和35年8月15日 第3種郵便物認可 ISSN 0009-2363

CHEMICAL & PHARMACEUTICAL BULLETIN

FEBRUARY 1989

VOL.37 NO.2
CPBTAL37(2)267-568(1989)

PHARMACEUTICAL SOCIETY OF JAPAN

Office of Secretary Pharmaceutical Society of Japan, 12–15–501, Shibuya 2-chome, Shibuya-ku, Tokyo 150, Japan

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The publication of this Journal was supported in part by a Grant-in-Aid for Publication of Scientific Research Result from the Ministry of Education, Science and Culture, which is gratefully acknowledge.

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Photochemical Iron(III)-Mediated Autoxidation of Dextromethorphan

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The photochemical reaction of dextromethorphan 1, a widely used anti-tussive drug, in hydrochloric acid and in the presence of iron(III) salts leads to the 10β-hydroxyderivative 3 as a major product in addition to the 10-ketoderivative 2. The product composition of this reaction is strongly dependent on the experimental conditions and the effects of solvents are presented.

Keywords photochemistry; heavy metal catalysis; autoxidation; stability; dextromethorphan

Dextromethorphan [3-methoxy-17-methyl-(9α,13α,14α)-morphinan, **1**) is a valuable non-narcotic anti-tussive drug in oral pharmaceutical form and its hydrobromide (**1a**) is described in several official Pharmacopeias. It has been known since 1956 that (**1a**) is moderately stable when exposed (3 d) in aqueous solution to direct sunlight, furnishing in a remarkably regioselective reaction the corresponding 10-ketoderivative (**2**)[1]; however, in our hands, we observed a fast photochemical reaction which was hard to reproduce. In accordance with the results of Brossi *et al.*,[1] Proska *et al.* have also recently reported the isolation of the 10-ketocompound from the oxygenated solutions of morphine.[2]

On the basis of some evidence, in particular the finding of traces of iron in glassware, we assumed that the reaction required catalysis by suitable inorganic ions. It is well known that Fe(III) ions and other higher valence metals act as efficient one-electron photo-oxidants in hydrochloric solutions, whereas photolysis of aqueous solutions of Fe(III) bromide produces bromine.[3] Here an interesting example has been reported by Barbier, who found that Fe(III)-induced photo-oxidation of benzylic methylenes in aqueous acetone occurs to yield the corresponding keto-compounds.[4]

In an effort to define the role of trace metals in these reactions, we have examined and report here the photochemical behavior of (**1a**) in the presence of Fe(III) in acidic solutions, and a plausible mechanistic sequence is proposed.

Results and Discussion

The irradiation of an aqueous or acidic solution of (**1a**) in the absence of Fe(III) ions did not induce any decomposition, irrespective of the presence or absence of molecular oxygen. By comparison, the irradiation (22 h) of a 2.68 mM solution of (**1a**) in 1 M hydrochloric acid in the presence of 6.2 mM Fe(III) chloride produced (at 85% conversion; high performance liquid chromatography (HPLC) analysis) a mixture of 10β-hydroxydextromethorphan (**3**) (61%) and the known 10-oxoderivative (**2**) (26%).

Compound **3** gave a molecular peak at *m/z* 287 by electron impact mass spectrum (EI-MS) and this value is in agreement with the molecular formula $C_{18}H_{25}NO_2$, indicating the presence of an additional oxygen atom. An inspection of the MS of **3** in comparison with that of **1** showed that the new oxygenated function cannot be located in the C- and D-rings since these are encompassed by fragment *m/z* 150 which remains undisplaced in the MS, whereas the peak at *m/z* 230 is displaced by 16 amu as compared to *m/z* 214 for **1**.[5] Accordingly, the infrared (IR) spectrum was devoid of any carbonyl absorption but had a discrete hydroxyl band at 3400 cm^{-1}. In the 200-MHz proton nuclear magnetic resonance (^{1}H-NMR) spectrum of **3**, the methine proton at C-9 was centered at 2.90 ppm (sharp doublet, J=2.5 Hz) whereas the signal of H-10 appeared as a singlet at 4.72 ppm. The remarkable low-field chemical shift position for this proton provided evidence for oxygen substitution at this site. The stereochemistry at C-10 as depicted in **3** was assigned by application of Karplus analysis[6] and the lack of any coupling for H-10 (dihedral angle of approximately 90°) indicated that the newly introduced OH group and aminomethylene bridge are *trans* to one another.

When we carried out the reaction on **1a** under the above conditions, no other hydroxy compound could be detected by ^{1}H-NMR spectroscopy, suggesting that **3** was being produced with complete control over the regio- and stereochemistry.

Evidence in support of the structure of the minor photoproduct (**2**) was secured by comparison with an authentic sample prepared according to Brossi *et al.*[1]

Additionally, we confirmed that the presence of externally added chloride ions (as hydrochloric acid) affected the efficiency of the photo degradation of **1a** induced by Fe(III) chloride in neutral or acidic solution. In the light of these results, the mechanism of the formation of **2** and **3** can be interpreted in terms of an initial benzylic hydrogen abstraction by Cl$^\cdot$ (Eq. 1) to generate the carbon-centered radical (**5**) (Eq. 2). Although the role of Cl$^\cdot$ as a radical initiator in photo-oxidation of organic compounds has been somewhat controversial,[7] the lack of reactivity in sulfuric acid solutions indicated that at least the formation of an Fe(III)–chloro complex is necessary for the reaction to take place (Eq. 1). Subsequent reaction of **5** with molecular oxygen leads to the secondary hydroperoxide (**6**) (Eqs. 3, 4) and this reactive transient species has several options of being transformed into final products. Thus, **6** can undergo dehydration, through O–O bond cleavage, to give the oxoderivative (**2**) (Eq. 5). However, this mechanism may only count for a minor part of the observed photodegradation and the formation of **3** could be rationalized by an alternative mechanism. The common intermediate (**6**) can under-

$$[FeX_n(H_2O)_{6-n}]^{3-n} \xrightarrow{h\nu} [FeX_{n-1}(H_2O)_{6-n}]^{3-n} + X^{\cdot} \quad (1)$$

$$\mathbf{1} + Cl^{\cdot} \longrightarrow \mathbf{5} + HCl \quad (2)$$

$$\mathbf{5} + {}^3O_2 \longrightarrow \mathbf{6} \quad (3)$$

$$\mathbf{1} + \mathbf{6} \longrightarrow \mathbf{5} + \mathbf{7} \quad (4)$$

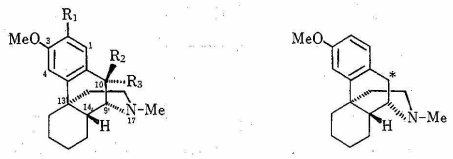
$$\mathbf{7} \longrightarrow \mathbf{2} + H_2O \quad (5)$$

$$\mathbf{7} + H^+ \longrightarrow \mathbf{8} + H_2O_2 \quad (6)$$

$$\mathbf{8} + H_2O \longrightarrow \mathbf{3} + H^+ \quad (7)$$

$$\mathbf{8} + MeOH \longrightarrow \mathbf{4} + H^+ \quad (8)$$

Chart 1



1 : R_1, R_2, R_3=H
2 : R_1=H; R_2, R_3=O
3 : R_1, R_3=H; R_2=OH
4 : R_1, R_3=H; R_2=OMe
6 : R_1, R_3=H; R_2=OO$^{\cdot}$
7 : R_1, R_3=H; R_2=OOH
9 : R_1, R_2=H; R_3=OH
10 : R_1=Br; R_2, R_3=H
5*=$\cdot$
8*=+

Fig. 1

go ionic decomposition *via* attack at the β-oxygen atom of the hydroperoxide function (C–O bond fission) with loss of a molecule of hydrogen peroxide (Eq. 6). This reaction predominates, in that the stability of the resulting carbenium ion (**8**) provides the driving force for this reaction, and subsequent quenching by a suitable nucleophilic solvent (*e.g.*, water) leads to **3**. Finally, carbocation trapping experiments were performed under the above conditions in the presence of 0.6 mM Fe(III) chloride in 1 : 1 methanol–2 M hydrochloric acid mixture and the corresponding methyl ether (**4**) was isolated in good yield (Eq. 8).

It is quite reasonable that the introduction of OH or OMe groups proceeded by entry from the sterically more accessible top face and a similar stereochemical outcome has recently been reported on morphinandienones.[8] Bottomside oxygen entry would be rather restricted especially because of the aminomethylene bridge. An unambiguous stereochemical assignment for **3** was accomplished by reduction of **2** with $LiAlH_4$ in refluxing tetrahydrofuran (THF). The sole isomer formed in this process is assigned the α-hydroxyl stereochemistry depicted in **9** since this is the expected result of hydride delivery from the least encumbered face of the carbonyl function in **2**.[1] Accordingly, the methine hydrogen at C-10 in **9** appears at 4.88 ppm [*vs.* 4.72 ppm in **3**] as a doublet (J=6.0 Hz) (*i.e.*, H-9 and H-10 are *cis*-oriented) and this assignment agrees with the generalization that an equatorial proton resonates at lower field than its axial epimer.[9]

By exposure of **1a** to sunlight in 1 M aqueous hydrobromic acid in the presence of Fe(III) ions we observed a rapid and clean transformation to 2-bromo-dextromethorphan (**10**) in 62% yield as the sole product. Compound **10** [$M^{+\cdot}$ 351/349(^{81}Br/^{79}Br)] was identified by spectral methods and unambiguous synthesis. In particular, the two aromatic protons appeared as singlets at 7.28 ppm (H-1) and 6.85 ppm (H-4) in the ^{1}H-NMR, thus confirming that substitution had occurred at the 2-position.

The difference in reactions between Cl$^{\cdot}$ and Br$^{\cdot}$ may be explained on the basis of frontier orbital theory; in the hydrogen-abstraction reactions, generally SOMO (singly occupied molecular orbital)/HOMO interaction-controlled, the SOMO energy of X$^{\cdot}$ lies between that of the HOMO (σ orbital of C–H bond) and the radical with the higher-energy SOMO will be less reactive than the one with the lower-energy SOMO.[10] This explains why the electrophilic Cl$^{\cdot}$ radical (SOMO energy: -13 eV)[11] reacts faster in hydrogen abstraction of the benzylic methylene than the Br$^{\cdot}$ radical (SOMO energy: -11.8 eV). In the light of these arguments, two bromine radicals would recombine to yield bromine and the expected electrophilic substitution at the A-ring of dextromethorphan would be cleanly observed as the exclusive reaction channel.

Experimental

Melting points were determined on a Buechi 510 apparatus and are uncorrected. The ^{1}H-NMR spectra were recorded on a Bruker WP-80 CW or on a Varian XL-200 spectrometer in $CDCl_3$ solutions with tetramethylsilane as an internal standard. Chemical shifts are reported in ppm (δ) and signal described as s (singlet), d (doublet), m (multiplet) or br (broad). Ultraviolet (UV) absorption spectra were recorded on a Beckman DU 6 spectrophotometer. EI-MS were measured on a Varian MAT 112 spectrometer. Silica gel chromatography (thin layer chromatography, TLC) was carried out on Merck pre-coated $60F_{254}$ plates. Preparative silica gel chromatography was performed on Merck pre-coated $60F_{254}$ (thickness: 1 mm, 20 × 20). HPLC analysis was performed on a Varian M 6000 pump, M 440 UV detector and 840 integrator system with 10 μm micro Bondapack C-18 column (i.d. 3.9 × 300 mm, Waters). The mobile phase was prepared by dissolving 5.8 g of dioctyl sulfosuccinate in water, MeOH, THF and concentrated H_3PO_4 330 : 630 : 37 : 1 and adjusting the pH to 3.30 with concentrated ammonia.[12]

Irradiation of 1a in HCl in the Presence of $FeCl_3$ Dextromethorphan hydrobromide (**1a**) (1.0 g, 2.68 mmol) was dissolved in 1 M HCl (1000 ml) containing $FeCl_3$ (1.0 g, 6.2 mmol) in ten different borosilicate vessels and irradiated with tungsten light (500 W, Philips PF 308 E/21) at 50 cm from the reaction vessels after saturation with oxygen. After 22 h, disodium ethylenediaminetetraacetic acid (EDTA) was added and the mixture was made alkaline with 10% ammonia and extracted with EtOAc (500 ml). The organic layer was washed with water (200 ml), dried and concentrated *in vacuo*. Preparative TLC (benzene–EtOH–10% ammonia, 89 : 10 : 1, one development, recovery with acetone) afforded the known 10-ketoderivative (**2**)[1] (Rf 0.45; 212 mg, 26%), the starting material (**1**) (Rf 0.29; 125 mg) and the amorphous 10β-hydroxydextromethorphan (**3**) (Rf 0.16; 500 mg, 61%). 10-Keto-3-methoxy-17-methyl-(9α,13α,14α)-morphinan (**2**): mp 188—189 °C (MeOH). UV $\lambda_{max}^{ethanol}$ nm (log ε): 287 (4.18), 231 (4.05). $[\alpha]_D^{20}$ −139 ° (c=3, $CHCl_3$). IR (KBr): 2930, 2850, 1665 cm^{-1}. ^{1}H-NMR: 1.0—2.8 (13H, m), 2.34 (3H, s, CH_3–N), 2.97 (1H, d, J=3.0 Hz, H-9), 3.88 (3H, s, CH_3–O), 6.90 (2H, m), 8.00 (1H, m). *Anal.* Calcd. for $C_{18}H_{23}NO_2$: C, 75.76; H, 8.12; N, 4.91. Found: C, 75.54; H, 8.19; N, 4.85.

10β-Hydroxy-3-methoxy-17-methyl-(9α,13α,14α)-morphinan (**3**): UV $\lambda_{max}^{ethanol}$ nm (log ε): 284 (3.20), 277 (3.22), 234 (3.92). IR (KBr): 3400, 2929, 2830 cm^{-1}. ^{1}H-NMR: 1.1—2.5 (13H, m), 2.49 (3H, s, N-CH_3), 2.90 (1H, d, J=2.5 Hz, H-9), 3.81 (3H, s, CH_3–O), 4.72 (1H, s, H-10), 6.80 (2H, m, H-2 and H-4), 7.42 (1H, m, H-1). MS m/z 287 ($M^{+\cdot}$), 230 ($M^{+\cdot} - C_2N_4NCH_3$), 150, 143.5 (M^{2+}).

(**9**) Hydrochloride: mp 184 °C (MeOH). IR (KBr): 3200, 1609, 1023 cm^{-1}. ^{1}H-NMR: 0.8—2.9 (14H, m), 2.96 (3H, s, CH_3–N), 3.5 (1H, m, H-9), 3.72 (3H, s, O–CH_3), 4.88 (1H, br d, J=6.0 Hz, H-10), 6.54 (1H, d, J=2.0 Hz, H-4), 6.88 (1H, dd, J=8.0, 2.0 Hz, H-2), 7.49 (1H, d, J=8.0 Hz, H-1). *Anal.* Calcd for $C_{18}H_{25}NO \cdot HCl \cdot 1/2H_2O$: C, 65.02; H, 8.19; N, 4.21. Found: C, 65.10; H, 8.22; N, 4.16.

Irradiation of 1a in HCl and MeOH in the Presence of $FeCl_3$ **1a** (1.5 g, 4 mmol) in a 1 : 1 mixture of MeOH and 2 M HCl (30 ml) containing $FeCl_3$ (3.2 mg, 0.02 mmol) in a borosilicate vessel was set aside at room temperature under direct sunlight for 24 h. After evaporation of half of the solvent, water (100 ml) was added and the mixture was made alkaline with 10% ammonia at 0 °C and extracted with dichloromethane (50 ml). The extract was washed with aqueous sodium potassium tartrate solution

(50 ml) and water (50 ml) and dried. Filtration and evaporation afforded a syrup (1.08 g), which was shown by TLC (benzene–EtOH–10% ammonia, 89 : 10 : 1) to contain the starting material, the 10-ketoderivative (**2**) and **3**, together with a new compound (*Rf* 0.38). Separation of this was achieved by careful preparative TLC using the same eluant and 250 mg (20%; 42% based on the recovered starting material) of pure 10β-methoxydextromethorphan (**4**) was isolated as an amorphous glass. UV $\lambda_{max}^{ethanol}$ nm (log ε): 284 (3.23), 277 (3.25). ^{1}H-NMR: 1.8—2.8 (13H, m), 2.49 (3H, s, CH_3–N), 3.51 (3H, s, O–CH_3), 3.78 (3H, s, O–CH_3), 4.12 (1H, s, H-10), 6.8 (2H, m), 7.3 (1H, m). MS *m/z* 301 ($M^{+\cdot}$), 271 ($M^{+\cdot} - OCH_2$), 150.5 (M^{2+}), 150 ($M^{+\cdot} - 151$).

Photochemical Synthesis of 2-Bromo-3-methoxy-17-methyl-(9α,13α,14α)-morphinan (10) **1a** (150 mg, 0.4 mmol) in 1 M HBr (100 ml) containing $FeCl_3$ (65 mg, 0.4 mmol) in a borosilicate vessel was exposed to direct sunlight for 4 h. The mixture was made alkaline with 10% ammonia and extracted with dichloromethane (50 ml). The extract was washed with 2% aqueous sodium EDTA solution (50 ml) and water (50 ml), dried and evaporated. The solid obtained was subjected to preparative TLC (CH_2Cl_2–MeOH–10% ammonia, 85 : 15 : 0.1) to give 93 mg (62%) of pure title compound (**10**). mp 130 °C (MeOH–H_2O). IR (KBr): 2906, 2855, 1595, 727, 712 cm^{-1}. ^{1}H-NMR: 1.0—3.0 (14H, m), 2.48 (3H, s, CH_3–N), 3.90 (3H, s, O–CH_3), 6.85 (1H, s, H-4), 7.26 (1H, s, H-1). *Anal.* Calcd for $C_{18}H_{24}BrNO$: C, 61.72; H, 6.90; N, 4.00. Found: C, 61.56; H, 6.88; N, 3.92.

The same compound was obtained in 38% yield according to the following procedure: **1a** (2.1 g, 5.6 mmol) was dissolved in 1 M HBr (50 ml) and water (200 ml) and bromine (2 g, 12 mmol) were added dropwise under stirring. After 4 h the solution was filtered and sodium bisulfite was added until the color disappeared. The solution was extracted with ethyl acetate (2 × 300 ml), dried and evaporated. The solid was dissolved in MeOH (40 ml) and precipitated with water (40 ml) giving 750 mg of a colorless crystalline solid (38%). This compound was identical with that obtained by the photochemical procedure.

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