Oxidation of Benzylic Carbon of 6,7-Benzomorphan

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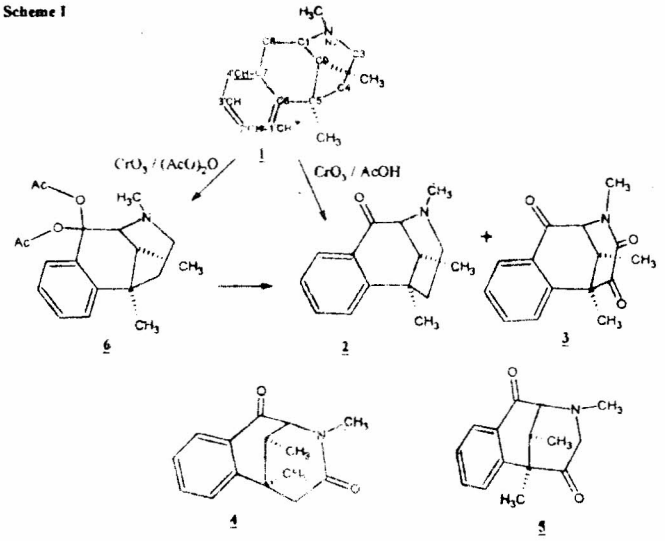
Abstract

The introduction of oxygen at the benzylic carbon of the 6,7-benzomorphan in improved yields was achieved by using acetic acid at room temperature. Various other oxidising agents which are known to attack benzylic methylene group were also investigated and reported.

Keywords *Analgesic, Benzomorphan, Benzomorphanones*

Scheme I



Introduction

Benzomorphanones provide useful intermediates which have been used for the synthesis of a variety of benzomorphan derivatives possessing profiles with respect to analgesic activity. As part of our continuing search for medicinally useful analgesics, it becomes necessary to have ready access to variously substituted benzomorphan-ones. The direct introduction of oxygen at the benzylic position in previously prepared benzomorphans by chromium trioxide oxidation in either aqueous sulphuric acid or acetic anhydride has been reported by Ziering, *et al.* (1970); Fauley and Lapidus, (1973). However in our hands, the oxidation of 2,5,9α-trimethyl-6,7-benzomorphan 1 using these processes gave low yields of the products largely due to incomplete oxidation. The procedure we employed involved the use of an excess solution of CrO_3 in acetic acid at room temperature.

Methodology

Chromic acid in 99% aqueous acetic acid was added drop-wise to the solution of 1 in glacial acetic acid over a period of several hours. When addition was complete, the reaction was stirred at room temperature for additional 20 hours. Efficient stirring was required for an optimum yield of the 2,5,9α-trimethyl-8-oxo-6,7-benzomorphan 2 .

Results and Discussion

This procedure gave a mixture of products as indicated by TLC. The main product required was 2 but some 2,5,9α–trimethyl-3,4,8-trioxo-6,7-benzomorph-an 3 and unreacted starting material were also isolated. The trioxo compound 3 was separated from the resulting mixture through its lower solubility in nonplolar solvents such as cyclohexane and petroleum ether. The infra-red spectrum of 3 exhibits absorption at υ_{max} 1690cm^{-1} and 1730cm^{-1} due to carbonyl function-alities. The PMR spectrum (Table I) shows eleven aliphatic

protons (δ1.0 – 4.0ppm). The C_9- and C_5-Methyl groups appear respectively as doublet and singlet at δ1.04 and δ1.67ppm, while the N-Methyl protons resonate at δ3.2ppm as expected. The remainder of the aliphatic protons C_1 and C_9 resonate at δ4.0ppm and δ2.8ppm respectively. The molecular ion observed at m/z 257 by mass spectrometry supports structure **3**.

Purification of 8-oxobenzomor-phan **2** was achieved by passing the crude material through a silica column (12:4:1, MeOH, DCM, AcOH). The IR, NMR, and mass spectra data confirmed the structure of **2**. Absorption at υ_{max} 1680cm^{-1} in infra-red spectrum of the product **2** suggested a conjugated carbonyl group.

A distinctive feature of the PMR spectrum of **2** is the lower-field position of the C_4' aromatic proton (δ8.03ppm) and the C_1 bridgehead proton (δ3.28ppm). The lower-field absorption indicates the deshielding effect of the carbonyl function on neighbouring protons which lie in the nodal region of the C=O bond. All aromatic protons in **2** are deshielded in comparison to **1**. The chemical shift difference between the aromatic protons results in a more complex aromatic signal than that of the starting material.

In ^{13}C NMR the carbonyl carbon, C_8, appeared as a singlet at the lowest field position (δ194.8ppm). Introduction of the electronegative oxygen at C_8 appreciably changes the local charge density of the adjacent carbon atom (Table II). The carbon-1 shifted down-field ≈10ppm in **2** compared with **1**.

Table I: 100Hz, ^{1}H NMR Chemical Shifts of 6,7-benzomorphan

	Aromatic - H					Aliphatic - H				
Compound	C_1'	C_2'	C_3'	C_4'	C_1-H	C_8		C_9-Me	C_5-Me	N-Me
	m					m		d	s	s
1	| ← 7.00 – 7.30 → |					2.38	3.20	0.85	1.35	2.35
	m			d		-				
2	7.20 – 7.70		8.30	3.28				0.85	1.40	2.35
3	7.40 – 7.80		8.20	4.00		-		1.04	1.67	3.20

Table II: ^{13}C NMR Chemical Shifts of 6,7-benzomorphan

	Aromatic - Carbon					
Compound	C_1'	C_2'	C_3'	C_4'	C_6	C_7
1	124.8	125.1	125.5	127.3	141.3	136.6
2	126.3	133.8	126.8	126.2	145.2	134.5

	Aliphatic - Carbon								
Compound	C_1	N-Me	C_3	C_4	C_5	C_5-Me	C_8	C_9	C_9-Me
1	95.5	42.7	47.5	42.7	35.9	25.5	23.6	42.1	14.1
2	69.2	43.1	47.6	42.7	36.1	26.0	194.8	42.7	15.0

Also it caused large down-field shift of the C_2' and C_6 resonance and up-field of C_1 and C_4'.

It is interesting that no dioxo compound (**4** or **5**) were detected. This suggest that attack at C-3 and C-4 occurs almost simultaneously. Oxidation at one of the methylene position probably increased the susceptibility of the adjacent carbon to oxidation.

The relative rates (Wiberg, 1965) of oxidation of primary, secondary and tertiary hydrogens are 1:110:7000. Reactions at tertiary C-H bond at the bridgehead in 6,7-benzomorphan is suppressed presumably because of the increase in strain associated with a change in hybridization at these positions.

The yield of **2** was optimised by varying the concentration of the reactants employed, the reaction time and the reaction temperature. At elevated temperature it was found to give higher yields of the trioxo-compound (**3**). Oxidation of **1** required slow addition of chromic acid solution over a longer time compared with 2,5-dimethyl-6,7-benzo-morphan (Hirani, 1983; PhD Thesis). The side product, was also formed in a larger quantity (18%) than in the case of 2,5-dimethyl-6,7-benzomorphan. The time course of this oxidation, which was followed by TLC, showed an initial rapid phase, followed by a slow and finally

cessation of reaction with the oxidation agent still remaining. The decrease in the rate of reaction with increasing time is probably due to the production of acetate ion during the reaction. Acetate is known to retard (Rocek and Borum, 1955) oxidation reaction. Further, the benzylic-type radical, the initial species involved in the oxidation of 6,7-benzomorphan is expected to form only slowly due to difficulty in its stabilization through overlap of the C-8 sp^2 hybridized orbital with the aromatic ring, a conclusion supported by examination of molecular models. Oxidation of CrO_3 varies with nature of chromium (IV) species employed but solvent also has a marked effect on the rate and the type of reaction which occurs (Wiberg, 1965). The use of chromium acetate to oxidise benzomor-phan gave 8,8-diacetate-6,7-benzomor-phan (**6**). An absorption peak at υ_{max} 1685cm^{-1} (C=O) 1740cm^{-1} (C=O) and 1230cm^{-1} (-COO-) in the infra-red spectrum together with the PMR spectrum support structure **6** as the product. The diacetate (**6**) was then hydrolysed with sulphuric acid in 50% ethanol to give **2** in a poor yield (below 10%).

Conclusion

Oxidation of **1** with CrO_3 in aqueous sulphuric acid gave a low yield of 8-oxobenzomorphan (**2**) largely due to incomplete oxidation. Further disadvantages of this method (Carr, 1976, PhD Thesis) compared to our method are the acid basic conditions which include refluxing the solution of benzomorphan in acetic chromic acid. Other oxidizing agents which are known to oxidise benzylic methylene groups were also investigated. The use of cerium (IV) ammonium nitrate (Syper, 1966) and or silver nitrate ammonium persulphate (Clark, *et al.* 1970) to oxidise **1** were ineffective as unreacted starting material were recovered in each case. Oxidation with 2.0 equivalents of dichlorodicyano-quinone (DDQ) (Findlay and Turner, 1971) in methanol also gave unreacted starting material and no trace of **2** was detected by IR. Several attempts made to oxidise **1** with DDQ by varying the condition of the reactants employed, the temperature and the reaction time were met with only limited successes.

Experimental

The infra-red spectra (liquid as films and solids as Nujol mulls) were recorded with a Unicam SP1025 spectro-meter and melting points (uncorrected) were taken on a Towson and Mercer melting point apparatus. Proton noise and off-resonance-decouple ^{13}C NMR spectra were recorded with a JOEL FX90Q spectrometer operating at 22.5MHz, and ^1H NMR spectra on a JOEL PS100 spectrometer operating at 100MHz. Samples were prepared in 5mm o.d. tubes as approximately 10% solution in $CDCl_3$ with Me_4Si as reference and deuterium of the solvents provided the lock signal for ^{13}C NMR. Mass spectra operating at 70eV (EI) and with Xe/glycerol for fast atom bombard-ment (FAB). The homogeneity of the compounds was checked by TLC on solid silica gel G plates.

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