Tetrahedron Letters,Vol.30,No.42,pp 5725-5728,1989 0040-4039/89 $3.00 + .00
Printed in Great Britain Pergamon Press plc

10-KETO OPIATES

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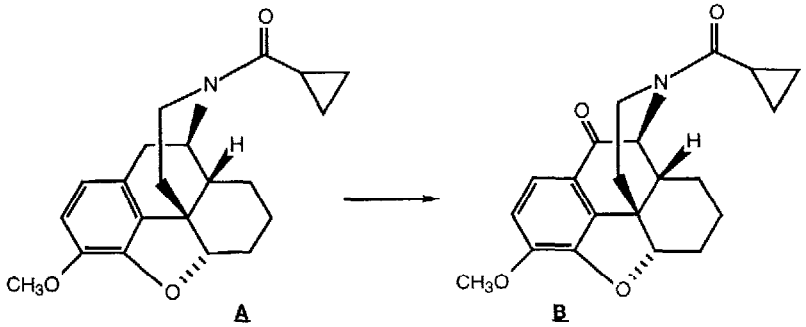
SUMMARY: The benzylic oxidation of *N*-cyclopropylcarbonylnordihydrodesoxy-codeine with selenium dioxide for the preparation of the 10-keto derivative is described.

In pursuit of our interest in κ selective analgesics, 10-keto-*N*-cyclopropylmethyl nordihydrodesoxymorphine was prepared. The critical reaction of the synthesis was the benzylic oxidation of *N*-cyclopropylcarbonylnordihydrodesoxycodeine (A). This article describes that transformation.



The literature revealed a few examples of benzylic oxidation of morphine-like structures. Introduction of oxygen at that position had been achieved by (a) chromic acid/dichromate oxidations [1] (b) oxidation of an exo double bond at the 10-position with ozone or osmium tetraoxide/sodium periodate [2] (c) electrochemical oxidation [3] (d) intramolecular ring formation [4] (e) nitration of thebaine using tetranitromethane and oxygen followed by base treatment [5], (f) photooxidation [6], and (g) vanadium(V) oxide oxidations [7].

Most of the methods were for specific substrates and not of general applicability. The chromic acid oxidation could have been used, but the conversion was low and obtaining substantial quantities of material was difficult.

For a practical synthesis, we investigated the benzylic oxidation using selenium dioxide. Heating 5.40 g of A with 4.61 g of selenium dioxide (Aldrich, Gold Label, 99.999%, ground under

nitrogen in a glove box) in 100 mL of dioxane at 180°C in a degassed sealed Carius tube for 24 hours gave 2.0 g (36% yield) of 10-keto-*N*-cyclopropylcarbonylnordihydrodesoxycodeine (B), m.p. 158-159°C; R*f*0.26 (silica gel, ether).

Isolation and purification were accomplished by flash chromatography on silica gel with ether-methylene chloride as eluent, followed with a short path distillation at $5x10^{-3}$ mm Hg (bath: 215°) and recrystallization from ethyl acetate after an activated carbon treatment. IR(KBr): 1685 (CO at C-10), 1635/1620 (amide CO) cm^{-1}; UV (CHCl3) λmax 325 mμ (ε=6000), 290 mμ (ε=13700); $[\alpha]_D^{25}$ (-) 297.3±0.8° (c 1.02, CHCl3); mass spec, m/z calcd: 353.1627; measured: 353.1626; Calcd. for C21H23NO4: C, 71.37; H, 6.56; N, 3.96. Found: C, 71.35; H, 6.52; N, 3.94.

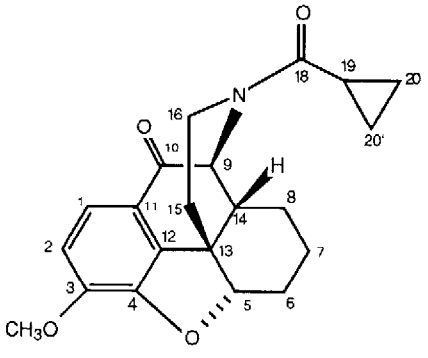
The NMR spectrum at ambient temperature indicated rotamers were present. Using ^1H and ^{13}C NMR spectra at elevated temperatures with ^{13}C DEPT, C-H correlations and ^1H COSY, the chemical shifts were assigned. [8,9]

The IR absorption at 1685 cm^{-1} is characteristic of an aromatic ketone and the u.v. absorption maxima and intensity are consistent with para-methoxy aromatic ketones [1a, 1b]. Coupled with the NMR spectra (see Table), the data established that the oxidation proceeded as indicated.

The scope of this oxidation is limited; using as substrates the *N*-methyl or *N*-cyano derivatives, only intractable materials were obtained, but the *N*-carboethoxy derivative could also be oxidized with selenium dioxide under the same conditions.

The conversion of B to 10-keto-*N*-cyclopropylmethylnordihydrodesoxymorphine and the results of pharmacological and receptor binding studies will be published elsewhere.

^1H and ^{13}C NMR Assignments



	^{13}C Chemical Shifts (ppm relative to TMS)					
	140° C in DMSO-D_6		30° C in DMSO-D_6		40 °C in $CDCl_3$	
Carbon	Multiplicity	Average	Rotamer A	Rotamer B	Rotamer A	Rotamer B
1	D	117.5	118.6	118.4	119.3	119.3
2	D	115.3	114.3	114.3	113.9	113.9
3	S	149.6	150.4	150.2	150.7	150.5
4	S	143.9	143.8	143.8	144.0	144.0
5	D	87.8	88.2	88.1	88.8	88.8
6	T	27.9	28.7	28.7	28.7	28.7
7	T	19.5	20.5	20.5	21.0	21.0
8	T	23.1	23.8	23.8	24.2	24.0
9	D	59.6	61.2	57.6	62.1	57.9
10	S	190.2	191.1	191.2	190.6	191.0
11	S	123.7	123.3	123.8	123.7	124.3
12	S	137.4	137.6	137.6	137.3	137.3
13	S	42.9	43.4	43.2	43.7	43.7
14	D	43.8	44.5	44.3	45.5	45.0
15	T	34.0	33.5	34.6	34.3	35.3
16	T	37.6	36.8	Unresolved	37.0	40.3
18	S	170.9	172.2	171.0	172.9	171.8
19	D	10.5	11.0	10.7	11.5	11.2
20	T	6.1, 5.9	7.7, 7.3	7.4, 7.0	7.6	7.1
OCH_3	Q	56.2	56.1	56.1	56.4	56.4

^{1}H Chemical Shifts (ppm relative to TMS)			
140° C in DMSO-D_6		30 °C in $CDCl_3$	
H	Average	Rotamer A	Rotamer B
1	7.33	7.46	7.46
2	7.01	6.93	6.93
5	4.73	4.73	4.73
6_{eq}	2.1	2.22	Unresolved
6_{ax}	1.18	1.29	Unresolved
7	1.50	1.70	Unresolved
7'	1.26	1.30	Unresolved
8_{eq}	1.67	1.78	1.71
8_{ax}	0.82	1.07	Unresolved
9	4.86	4.73	5.31
14	2.28	2.35	2.20
15	1.95	1.97	2.00
15'	1.85	1.90	2.00
16_{eq}	4.27	4.55	4.18
16_{ax}	2.75	2.70	3.23
19	2.00	2.19	Unresolved
20	0.8, 0.7	1.0 - 0.8	1.0 - 0.8
OCH_3	3.96	3.98	3.98

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(Received in USA 28 August 1989)