10-Ketonaltrexone and 10-Ketooxymorphone

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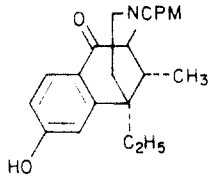
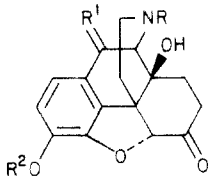
Ethylketocyclazocine (1) has greater κ/μ selectivity than cyclazocine in brain binding assays. 10-Ketonaltrexone (11) and 10-ketooxymorphone (10) were prepared from naltrexone 3-methyl ether and oxycodone, respectively. Bioassays in the myenteric plexus longitudinal muscle preparation of the guinea pig ileum and in the mouse vas deferens, in addition to brain binding assays, demonstrated that 10 and 11 were far less potent than naltrexone (2) and oxymorphone (3) at μ sites and also had little affinity for κ and δ sites. It is concluded that introduction of the 10-keto group in naltrexone and oxymorphone diminished opioid effects at all binding sites.

Ethylketocyclazocine (1, EKC) differs structurally from cyclazocine in having a keto group at C-1 and an ethyl rather than a methyl group at C-6. The κ/μ selectivity of EKC is greater than that of cyclazocine.[1] Naltrexone (2) is a potent opioid antagonist with little agonist activity.[2] The *N*-methyl analogue oxymorphone (3) is a classical morphine-like agonist.[3] In this paper, we describe the preparation of the 10-keto analogues 10 and 11 of oxymorphone and naltrexone and some of their pharmacological properties.



1, CPM = cyclopropylmethyl



2, R=CPM; $R^1=H_2$; R^2=H (naltrexone)
3, R=CH_3; $R^1=H_2$; R^2=H (oxymorphone)
4, R=CH_3; $R^1=H_2$; $R^2=CH_3$ (oxycodone)
5, R=CH_3; R^1=  ; $R^2=CH_3$
6, R=CH_3; R^1=O; $R^2=CH_3$
7, R=CPM; $R^1=H_2$; $R^2=CH_3$
8, R=CPM; R^1=  ; $R^2=CH_3$
9, R=CPM; R^1=O; $R^2=CH_3$
10, R=CH_3; R^1=O; R^2=H
11, R=CPM; R^1=O; R^2=H

Several years ago, Rapoport studied the CrO_3 oxidation in dilute H_2SO_4 of codeine and some of its congeners.[4] In each case the corresponding 10α-hydroxy analogues were obtained accompanied by large amounts of recovered starting material. Very low yields of the corresponding keto compounds were realized. Using similar conditions with oxycodone as the substrate, we isolated the 10α-OH analogue 5, which was formed in 4.2% yield, and the corresponding 10-keto derivative 6, which was isolated in 4.6% yield. The configuration of the 10α-OH was assigned on the basis of NMR spectroscopy.[5,6] A similar oxidation of naltrexone 3-methyl ether gave 8 and 9 in 6.4% and 2.3% yield, respectively.

Because of these low yields, other oxidizing agents were investigated. In the case of oxycodone, the best of these was the CrO_3–3,5-dimethylpyrazole (CrO_3–DMP) complex.[7] This reagent gave 6 in 18.5% yield along with 29% of recovered oxycodone. Unfortunately, when naltrexone 3-methyl ether was the substrate, there was no improvement in the yield of 9.

Table I. Antagonist Effects of Naltrexone and Ketonaltrexone at μ and κ Receptors in the Guinea Pig Ileum Longitudinal Muscle Myenteric Plexus and at μ, κ, and δ Receptors in the Mouse Vas Deferens Preparations

	dose ratio[a] due to antagonist effects of		
	naltrexone, 100 nM	ketonaltrexone	
		100 nM	1000 nM
guinea pig myenteric plexus			
normorphine (μ)	276.0 ± 55.2	1.84 ± 0.26	
ethylketazocine (κ)	23.9 ± 5.5	1.58 ± 1.10	
mouse vas deferens			
normorphine (μ)	50.2 ± 7.79	0.57 ± 0.09	
ethylketazocine (κ)	15.5 ± 4.04	0.93 ± 0.10	
(D-Ala^2,D-Leu^5)enkephalin (δ)	4.19 ± 0.35		0.71 ± 0.04

[a] The values are the means ± SEM of three to five separate experiments. IC_{50} values from the agonist were determined prior to and following a 10-min incubation with the antagonist. The change in IC_{50} was expressed as the dose ratio = IC_{50} postantagonist – IC_{50} preantagonist.

Table II. Agonist Activity of Oxymorphone and Ketooxymorphone in the Guinea Pig Ileum Longitudinal Muscle Myenteric Plexus and the Mouse Vas Deferens Preparations

	agonist act.: IC_{50}, nM	
preparation	oxymorphone	ketooxymorphone
guinea pig myenteric plexus	24	>1000
mouse vas deferens	77	>1000

Oxidation of either 5 or 8 with MnO_2 was very sluggish. Oxidation of these alcohols with CrO_3–DMP was complete in 15 min and gave the desired keto compounds 6 and 9 in high yield. The rapid reactions of this reagent with 5 can account for the fact that none of this alcohol was isolated during the CrO_3–DMP oxidation of 4 to 6. Demethylation of 6 and 9 with BBr_3 gave the corresponding

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Table III. Inhibitory Binding Constants of Compounds in Guinea Pig Brain Homogenates Reported as K_i Values in nM[a]

compd	μ site	δ site	κ site
naltrexone	1.08 ± 0.17	6.6 ± 0.08	8.5 ± 0.82
10-ketonaltrexone	31.1	281	102
oxymorphone	0.78 ± 0.05	50 ± 11	137 ± 19
10-ketooxymorphone	19% inhibn at 640 nM	6% inhibn at 3200 nM	17% inhibn at 6400 nM

[a] The μ site was labeled with [^{3}H]-(D-Ala^2,MePhe^4,Gly-ol^5)enkephalin (1 nM), the δ site with [^{3}H]-(D-Ala^2,D-Leu^5)enkephalin (0.7 nM) after suppression of μ binding and the κ site with (-)-[^{3}H]-bremazocine (0.1 nM) after suppression of μ and δ binding. All experiments were carried out at 25 °C.

3-hydroxy compounds **10** and **11** in moderate yields.

Biological Results

μ, κ, and δ binding was determined in guinea pig brain membranes by using the method of Corbett et al.[8] Opioid agonist and antagonist potency was evaluated in the myenteric plexus longitudinal muscle of the guinea pig ileum and the mouse vas deferens preparation.[9,10]

In bioassays, the antagonist properties of naltrexone at μ, κ, and δ receptors were markedly attenuated by substitution of the 10-keto group (Table I). Substitution of the 10-keto group attenuated the agonist properties of oxymorphone also (Table II).

Consistent with the effects of 10-keto substitution on the actions of naltrexone and oxymorphone in the isolated tissue preparations, in binding assays the 10-keto-substituted compounds possessed much lower affinities for μ, κ, and δ binding sites than those of the parent compounds **2** and **3** (Table III).

Discussion

In all the assays carried out with **10** and **11**, the opioid activity was markedly lower than that of the parent compounds **2** and **3**. In contrast, EKC had the same potency as cyclazocine at κ sites but was much weaker at μ sites.[1] The introduction of the keto group at the benzylic carbon of oxymorphone and naltrexone not only decreased μ activity but in the case of the latter antagonist activity at the other sites was reduced also. It appears that the primary effect of introducing a keto group at the benzylic carbon in the morphine structures is to markedly reduce agonist and antagonist potency.

Experimental Section

Melting points were taken on a Mel-Temp apparatus and are corrected. The ^{1}H NMR spectra were run on 200-MHz Varian XL 200 and 60-MHz Hitachi Perkin-Elmer R-600 spectrometers using $CDCl_3$ as the solvent with $(CH_3)_4Si$ as the internal standard. IR spectra were run in KBr pellets on a Perkin-Elmer 298 infrared spectrometer and the mass spectra were run on a JEOL-0150 instrument at the Sterling-Winthrop Research Institute. We thank Dr. S. Clemens and C. Martini for these determinations. Microanalyses were performed by Spang Microanalytical Laboratory, Eagle Harbor, MI. All analytical results were within ±0.15% of the calculated values. Methylation of naltrexone to give **7** was carried out with dimethyl sulfate in NaOH solution in 96% yield, mp 91–93 °C.

10α-Hydroxyoxycodone (5) and 10-Ketooxycodone (6): Oxidation of Oxycodone. A. CrO_3–H_2SO_4. A solution of 2.00 g (6.34 mmol) of oxycodone (**4**) in 40 mL of 1.5 N H_2SO_4 was stirred at room temperature while 1.27 g (12.7 mmol) of CrO_3 was added portionwise over a period of 30 min. To this orange suspension was added dropwise 3.11 g of concentrated H_2SO_4 over a 30-min period and the reaction mixture was stirred for 28 h at room temperature. The mixture was cooled in an ice–salt bath and made slightly alkaline by the cautious addition of 25% NaOH. The suspension wa thoroughly extracted with a $CHCl_3$–CH_3OH (4:1) solution, and the organic extracts were combined and evaporated to leave a residue (weight 1.23 g), which was chromatographed on silica gel. Elution with $CHCl_3$ gave 96 mg (4.6%) of 10-ketooxycodone (**6**), mp 237–240 °C. Further elution afforded 574 mg of recovered oxycodone.

After recrystallization from CH_3OH, **6** melted at 242–243 °C. IR 3340 (OH), 1720 (C=O at C-6), 1668 cm^{-1} (C=O at C-10); NMR δ 1.45–1.70 (m, 2 H, H-15), 1.70–1.98 (m, 2 H, H-8), 2.00–3.20 (m, 4 H, H-16, H-7), 2.49 (s, 3 H, NCH_3), 3.01 (s, 1 H, H-9), 4.03 (s, 3 H, OCH_3), 4.76 (s, 1 H, H-5β), 4.82 (br s, 1 H, H-14β-OH, exchangeable with D_2O), 6.87 (d, 1 H, J = 9 Hz, H-2), 7.47 (d, 1 H, J = 9 Hz, H-1); MS, m/e 329 (M^+) (calcd mass 329.4). Anal. C, H. N.

Further elution with $CHCl_3$–CH_3OH (19:1) furnished 319 mg of a mixture, which was separated on preparative TLC plates (silica gel) with use of the same solvent mixture for development. An additional 80 mg of **4** was recovered (total recovery 654 mg, 32.7%) and there was obtained 89 mg (4.2%) of 10α-hydroxyoxycodone, mp 241–243 °C, after recrystallization from CH_3OH. IR 3520 (OH at 10α), 3350 (OH at 14β), 1705 cm^{-1} (C=O at C-6); NMR δ 1.40–1.74 (br m, 2 H, H-15, U H, OH at C-10 or at C-14, exchangeable with D_2O), 1.75–2.85 (m, 6 H, H-8, H-16, H-7), 2.55 (s, 3 H, NCH_3), 2.90 (d, 1 H, H-9), 3.50 (s, 1 H, OH at C-10 or at C-14, exchangeable with D_2O), 3.95 (s, 3 H, OCH_3), 4.68 (s, 1 H, H-5β), 5.10 (br d, 1 H, H-10β, collapsed to a singlet after treatment with D_2O), 6.90 (m, 2 H aromatic H); MS, m/e 331 (M^+) (calcd mass 331.4). Anal. C, H. N.

B. CrO_3–3,5-Dimethylpyrazole (DMP). To a stirred suspension of 3.24 g (32.4 mmol) of CrO_3 in dry CH_2Cl_2 kept at -15 °C was added 3.08 g (32.0 mmol) of DMP. The dark complex was stirred for 1 h and then 500 mg (1.59 mmol) of oxycodone (**4**) was added. Stirring was continued for 4 h at -10 °C (±5 °C) and then the mixture was kept at -20 °C for 16 h. The cold mixture was treated with 25 mL of 10% NaOH and after 1 h the organic phase was separated. The aqueous layer was extracted with $CHCl_3$ and the whole was filtered through a bed of Celite to break the emulsion. The $CHCl_3$ was separated and the aqueous phase was neutralized with HCl before being shaken with $CHCl_3$–CH_3OH (9:1). The combined organic extracts were evaporated to dryness to leave a residue (3.22 g), which was sublimed at 50 °C (0.02 torr) to remove DMP: weight 2.6 g (84%), mp 105–107 °C. The residue was chromatographed on silica gel with $CHCl_3$ as the eluant. There was obtained 97 mg (18.5%) of 10-ketooxycodone (**6**), mp 237–240 °C. Further elution with $CHcl_3$–CH_3OH (20:1) gave 148 mg (29.6%) of recovered oxycodone.

10-Hydroxynaltrexone 3-Methyl Ether (8) and 10-Ketonaltrexone 3-Methyl Ether (9). The same procedure described in A for oxycodone was used. The quantities were as follows: 6.08 g (0.060 mol) of CrO_3, 10.8 g (0.03 mol) of naltrexone-3-methyl ether (**7**) 400 mL of 1.5 N H_2SO_4, and 29.4 g of concentrated H_2SO_4. After 28 h at 25 °C the solution was neutralized, extracted, concentrated, and chromatographed to furnish 250 mg (2.3%) of **9**: mp 109–110 °C after crystallization from hexane; IR 3400 (OH), 1723 (C=O at C-6), 1668 cm^{-1} (C=O at C-10); NMR δ 0.03–0.20, 0.28–0.42, 0.44–0.66, 0.74–1.04 (4 m, 5 H, c-C_3H_5), 1.48–1.84 (m, 3 H, H-15, H-14β-OH, one proton exchangeable with D_2O), 1.90–2.22 (m, 2 H, H-8), 2.27–2.44 (m, 2 H, H-16), 2.50–2.80 (m, 2 H, H-17), 2.84–3.20 (m, 2 H, H-7), 3.34 (s, 1 H, H-9), 4.02 (s, 3 H, OCH_3), 4.80 (s, 1 H, H-5β), 6.92 (d, 1 H, H-2), 7.45 (d, 1 H, H-1); MS, m/e 369.1 (M^+) (calcd mass 369.4). Anal. C, H, N.

Further elution with $CHCl_3$ gave 2.74 g (25.3%) of almost pure **7**. Elution with $CHCl_3$–CH_3OH (99:1) gave a solid, which after chromatography on preparative TLC plates (silica gel, $CHCl_3$–CH_3OH, 97:3) afforded 726 mg (6.4%) of **8**: mp 184–185 °C after crystallization from CH_3OH; IR 3490 (10α-OH), 3350 (14β-OH), 1715 cm^{-1} (C=O at C-6); NMR δ 0.06–0.34, 0.46–0.70, 0.72–1.04 (3 m, 5 H, c-C_3H_5), 1.40–1.90 (m, 3 H, H-15, H-10-OH, one proton exchangeable with D_2O), 1.94–2.13 (m, 2 H, H-8), 2.24–2.48 (m,

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2 H, H-16), 250–2.62 (m, 2 H, H-17), 2.62–2.76 (m, 1 H, H-7α?, 2.90–3.31 (m, 1 H, H-7β?), 3.25 (s, 1 H, H-9), 3.94 (s, 3 H, OCH_3), 4.73 (s, 1 H, H-5β), 5.04 (d, 1 H, H-10β, collapsed to a singlet after treatment with D_2O), 5.13 (s, 1 H, 14β-OH exchangeable with D_2O), 6.90 (m, 2 H, H-1, H-2); MS, *m/e* 371.2 (M^+) (calcd mass 371.4). Anal. C, H. N.

Oxidation of 5 and 8 with CrO_3–DMP. The CrO_3–DMP complex was prepared from 7.4 mg (0.077 mmol) of DMP, 7.6 mg (0.076 mmol) of CrO_3, and 1.0 mL of CH_2Cl_2.[7] After 20 min 10 mg (0.030 mmol) of **5** was added. Fifteen minutes later, the mixture was worked up as described above to give 7 mg of **6**, mp 236–239 °C, identical in all respects with an authentic sample.

Similarly oxidation of 10 mg of **8** gave 9.2 mg of **9**, mp 108–110 °C after crystallization from hexane.

10-Ketooxymorphone (10). A solution of 0.84 mL (8.78 mmol) of BBr_3 in 10 mL of dry $CHCl_3$ was added in one portion to a stirred solution of 240 mg (0.73 mmol) of **6** in 40 mL of dry $CHCl_3$ at room temperature. After 43 h a solution of 15 mL of concentrated NH_4OH in 15 mL of H_2O was added and stirring was continued for 45 min. The $CHCl_3$ layer was separated and washed with 20 mL of the diluted NH_4OH and then with H_2O. Evaporation of the $CHCl_3$ gave 57 mg (24%) of crude starting material, which was purified with the aid of preparative TLC (silica gel and $CHCl_3$ as the eluant).

The combined NH_4OH solutions were cooled to −5 °C (ice–salt bath) and carefully neutralized with HCl. The pH was adjusted to 7 with $NaHCO_3$ solution and the mixture was extracted several times with $CHCl_3$. Evaporation of the combined extracts left 117 mg (51%) of **10**, mp 250–253 °C dec. After crystallization from benzene, there was obtained 85 mg (37%) of the analytically pure sample: mp 246–248 °C dec; IR 3650–3000 (3-OH and 14β-OH), 1720 (C=O at C-6), 1670 cm^{-1} (C=O at C-10); NMR δ 1.50–1.73 (t, 2 H, H-15), 1.75–2.00 (m, 2 H, H-8), 2.00–3.20 (m, 4 H, H-16, H-7), 2.50 (s, 3 H, NCH_3), 3.02 (s, 1 H, H-9), 3.50–4.60 (br s, 2 H, 3-OH, 14β-OH, exchangeable with D_2O), 4.80 (s, 1 H, H-5β), 6.90 (d, 1 H, *J* = 9 Hz, H-2), 7.44 (d, 1 H, *J* = 9 Hz, H-1); MS, *m/e* 315 (M^+) (calcd mass 315.3). Anal. C, H. N.

10-Ketonaltrexone (11). The reagents used were 0.75 mL (7.8 mmol) of BBr_3 in 50 mL of dry $CHCl_3$ and 240 mg (0.65 mmol) of **9**. After 43 h the mixture was worked up as described directly above. The $CHCl_3$ layers gave 81 mg (34%) of unreacted **9** and the NH_4OH layers furnished 113 mg (49%) of almost pure 10-ketonaltrexone, which after crystallization from benzene afforded 88 mg (38%) of pure 10-ketonaltrexone, which decomposed over the range 135–180 °C: IR 3640–3000 (3-OH, 14β-OH), 1720 (C=O at C-6) 1669 cm^{-1} (C=O at C-10); NMR δ 0.04–0.22, 0.28–0.42, 0.44–0.60, 0.80–1.08 (4 m, 5 H, c-C_3H_5), 1.50–1.84 (m, 2 H, H-15), 1.88–2.24 (m, 2 H, H-8), 2.24–2.45 (m, 2 H, H-16 or H-17), 2.50–2.80 (m, 2 H, H-16 or H-17), 2.80–3.24 (m, 2 H, H-7), 3.36 (s, 1 H, H-9), 4.84 (s, 1 H, H-5β), 6.94 (d, 1 H, H-2), 7.42 (d, 1 H, H-1); MS, *m/e* 355 (M^+) (calcd M 355.4). Anal. C, H. N.

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Registry No. **2**, 16590-41-3; **3**, 76-41-5; **4**, 76-42-6; **5**, 96453-12-2; **6**, 96445-11-3; **7**, 16617-07-5; **8**, 96445-12-4; **9**, 96445-13-5; **10**, 96445-15-7; **11**, 96445-14-6.

Book Reviews

Clinical Pharmacy Education and Patient Education: Proceedings of the 12th European Symposium on Clinical Pharmacy, Barcelona, 1983. Progress in Clinical Pharmacy. (Volume I). Edited by Joaquin Bonal and J. W. Poston. Cambridge University Press, Cambridge. 1984. xiv + 322 pp. 16 × 23.5 cm. ISBN 0-521-26610-6. $49.50.

This volume presents selected papers from the 12th European Symposium on Clinical Pharmacy conducted in Barcelona, Spain, in October 1983. The meeting was held together with the XXVIII Congress of the Spanish Society of Hospital Pharmacists. It is not suprising, therefore, that the topics predominately represent current issues in hospital pharmacy practice in Europe.

The major themes of the meeting are reflected in the title of the proceedings. About one-third of the textbook is devoted to papers dealing with patient education programs or undergraduate and postgraduate educational programs in clinical pharmacy in Europe and the United States. For American pharmacy educators, these papers can provide an interesting comparison of the sequencing and implementing of educational programs in the various countries. A few of these papers address efforts toward integrating clinical pharmacy services in community practice.

The balance of the volume presents numerous papers of original research on a wide range of topics in clinical pharmacy. These papers are brief, averaging four pages double-spaced, and are referenced. They vary considerably in rigor of study design and patient population size. Due to these shortcomings, many papers can only be considered preliminary reports. Topics in the administrative area include drug utilization studies, technician training programs, unit dose, and computerization of routine pharmacy functions. These papers offer few, if any, new ideas for American hospital pharmacy practitioners. Several articles report intravenous admixture stability studies especially for chemotherapeutic agents and total parenteral nutrition. Case reports and studies appear on adverse drug reactions associated with total parenteral nutrition, narcotics, and diuretics. A substantial number of papers present clinical pharmacokinetic studies of antibiotics, anticonvulsants, and chemotherapeutic agents in the presence of disease states. Some of this material presents new knowledge in the field, especially for drugs which are not commercially available in the United States (for example, the antibiotic ceftazidime) or are dosed in a manner not commonly employed (for example, epidural or intrathecal administration of morphine).

This symposium proceedings can provide American pharmacy educators–practitioners with an interesting comparison of state-of-the-art practice and education in Europe and the United States. The noticeable omission of a subject or author index impedes the reader from quickly accessing information. For practitioners specializing in oncology, neurology, or infectious diseases, the research reports can provide a brief overview of clinical trials and pharmacokinetic studies conducted by their international pharmacy colleagues.

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Phosphorus-31 NMR. PRINCIPLES AND APPLICATIONS. Edited by David G. Gorenstein. Academic Press, Orlando, FL. 1984. xiv + 604 pp. 16 × 23.5 cm. ISBN 0-12-291750-2. $79.00.

This book is a superbly edited collection of 18 chapters from experts on ^{31}P NMR. Five of the chapters were written by the editor, David G. Gorenstein. Gorenstein contributed the first two chapters, which provide a well-balanced discussion of ^{31}P chemical shifts and coupling constants in relation to theoretical treatments, and the final chapter, which is an appendix of shift and coupling data for selected compounds. All of the other chapters, with the