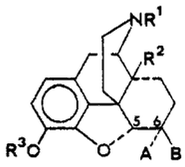
Table I. NMR Spectral Data of 6-Substituted Desomorphines



				A = R⁴; B = H		A = H; B = R⁴	
R¹	R²	R³	R⁴	5β-H, δ	$J_{5\beta-6\beta}$, Hz	5β-H, δ	$J_{5\beta-6\alpha}$, Hz
CH_3	H	CH_3	OH[d]	4.58	5.1	4.34	6.0
CH_3	H	CH_3	OAc[d]	4.59	5.7	4.43	6.5
CH_2-c-C_3H_5	OH	H	OH[e]	4.64	4.0	4.53	6.0
$CH_2CH{=}CH_2$	OH	H	OH[c]	4.62	4.0	4.52	6.0
CH_2-c-C_3H_5	OH	H	NH_2[b]	4.68	4.0	4.28	7.4
$CH_2CH{=}CH_2$	OH	H	NH_2[b]	4.55	4.0	4.28	7.4
CH_3	OH	H	NH_2[a]	4.64	3.2	4.28	6.8

[a] This work. [b] Reference 5. [c] Reference 12. [d] Reference 14. [e] Reference 17.

in anhydrous EtOH (150 mL). The mixture was stirred 8 h under dry N_2, diluted with MeOH (100 mL), and filtered. The residue obtained after removal of solvent was partitioned between $CHCl_3$ and 3% aqueous NH_4OH. The combined $CHCl_3$ extracts were taken to dryness and the residue was crystallized from 75% aqueous EtOH, affording two crops of slightly impure **10b**. This material was purified by conversion to the dihydrochloride, which was crystallized from ethanol–acetone (9:1), and then reconverted to the free base. Recrystallization from 75% aqueous EtOH yielded 1.71 g (60%) of pure **10b**: mp 238–240 °C; $[\alpha]^{25}_D$ −211° (*c* 1.2, $CHCl_3$); R_f 0.69; mass spectrum (70 eV), *m/e* 482 (M^+, 8.5%); NMR (deuterium-exchanged free base in $CDCl_3$) δ 6.54 and 6.36 (2 d, 1 H each, *J* = 8.1 Hz, Ar H), 4.66 (d, 1 H, *J* = 7.4 Hz, C_5-H).

Anal. Calcd for $C_{31}H_{34}N_2O_3$: C, 77.15; H, 7.10; N, 5.80. Found: C, 76.82; H, 7.24; N, 5.83.

Hydrogenolysis of **10b**·2HCl (2.17 g, 3.9 mmol) was conducted at 40 psi in MeOH with 0.25 g of 5% Pd/C for 3 days and then with an additional 0.25 g of catalyst for 2 more days. The catalyst was filtered, the filtrate was taken to dryness, and the residue was recrystallized from methanol–2-propanol–toluene (1:8:1). The yield of two crops of **3b**·2HCl was 1.4 g (95%): mp >260 °C; $[\alpha]^{25}_D$ −91.1° (*c* 1.3, H_2O); R_f 0.24; mass spectrum (70 eV), *m/e* 302 (M^+, 59%); NMR (deuterium-exchanged free base in $CDCl_3$) δ 6.64 and 6.53 (2 d, 1 H each, *J* = 8.0 Hz, Ar H), 4.28 (d, 1 H, *J* = 6.8 Hz, C_5-H).

Anal. Calcd for $C_{17}H_{24}N_2O_3Cl_2{\cdot}CH_3OH$: C, 53.08; H, 6.93; N, 6.88. Found: C, 52.84; H, 7.18; N, 6.94.

6α-Amino-14-hydroxydesomorphine (α-Oxymorphamine, 4b). A benzene solution (150 mL) containing oxymorphone base (2.5 g, 8.3 mmol), benzylamine (1.0 g, 9.3 mmol), and a trace of *p*-toluenesulfonic acid was refluxed for 10 h, using a Dean–Stark trap for azeotropic removal of water. The mixture was then concentrated (30 mL) at 1 atm, and a solution of $NaBH_4$ (0.12 g, 3 mmol) in absolute EtOH (80 mL) was added.[19] After being stirred under N_2 for 3 h, the resulting solution was diluted with H_2O and concentrated to remove most of the EtOH. Further dilution with H_2O, basification (NH_4OH), extraction ($CHCl_3$), and concentration of the organic phase afforded crude **11b** (R_f 0.58). This was dissolved in MeOH (150 mL) and concentrated HCl was added to pH 2. Hydrogenation was conducted at 40 psi with 0.8 g of 5% Pd/C for 3 days and then with an additional 0.5 g of 5% Pd/C for 3 more days. The catalyst was filtered, the filtrate was taken to dryness, and the residue was recrystallized from methanol–2-propanol–toluene (1:8:1), yielding 1.8 g of **4b**·2HCl (57%): mp >260 °C; $[\alpha]^{25}_D$ −144° (*c* 1.4, H_2O); R_f 0.15; mass spectrum (70 eV), *m/e* 302 (M^+, 87%); NMR (deuterium-exchanged free base in $CDCl_3$) δ 6.71 and 6.48 (2 d, 1 H each, *J* = 8.0 Hz, Ar H), 4.64 (d, 1 H, *J* = 3.2 Hz, C_5-H).

Anal. Calcd for $C_{17}H_{24}N_2O_3Cl_2{\cdot}0.5CH_3OH$: C, 53.71; H, 6.70; N, 7.16. Found: C, 53.25; H, 7.06; N, 7.49.

(19) Treatment with $NaBH_4$ does not reduce the imine **11** but does prevent the accumulation of an unknown byproduct, during the subsequent hydrogenation, which causes poisoning of the catalyst.

6α-Amino-14-hydroxy-17-(cyclopropylmethyl)nordesomorphine (α-Naltrexamine, 4a). By use of the same procedure as described for **4b** above, **4a**·2HCl,[5] mp >260 °C, R_f 0.19, was prepared in 76% yield (first crop).

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Registry No. **1a**·HCl, 16676-29-2; **1b**, 76-41-5; **3a**·2HCl, 63463-07-0; **3b**·2HCl, 73986-22-8; **4a**·2HCl, 63463-06-9; **4b**·2HCl, 73986-23-9; **10a**, 73986-24-0; **10b**, 73986-25-1; **10b**·2HCl, 73986-26-2; **11b**, 73986-27-3; dibenzylamine, 103-49-1.

O-Alkylation of 2-(Carbomethoxy)cyclopentanone

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The alkylation of ambident anions generated from β-keto esters has been extensively studied,[1-14] especially in

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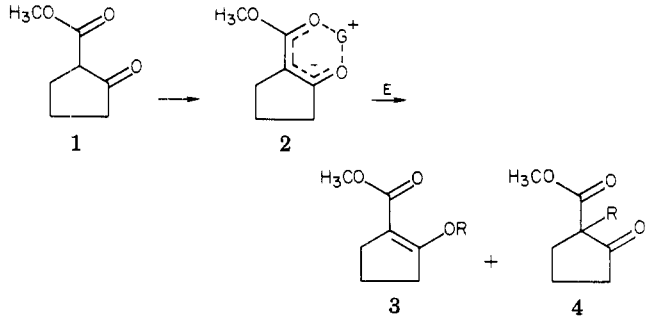
Table I. Alkylation of the Enolate of Methyl 2-Oxocyclopentanecarboxylate in Hexamethylphosphoramide

no.	gegenion (G)	electrophile (E)	T, °C (t, h)	O-/C-alkylation[a] ratio (yield, %)[b]
1	K^+	$(C_2H_5O)_2SO_2$	25 (12)	65/35 (70)
2	K^+	$(C_2H_5O)_2SO_2$	90 (1)	64/36 (40)
3	K^+	$C_2H_5OSO_2C_6H_4$-p-CH_3	60 (1)	65/35 (50)
4	K^+	$(C_2H_5)_3O^+BF_4^-$	25 (3.5) or 90 (0.5)	~85/15 (55)
5	K^+	$C_2H_5OSO_2C_6H_3$-2,4-$(NO_2)_2$	25 (20)	80/20 (35)
6	K^+	$(CH_3)_2CHOSO_2C_6H_4$-p-CH_3	90 (1.5)	75/25 (55)
7	n-Bu_4N^+	$(CH_3)_2CHOSO_2C_6H_4$-p-CH_3	90 (1)	80/20 (70)
8	K^+	$CH_2=CHCH_2Cl$	25 (24) or 90 (0.5)	~10/90 (75)
9	K^+	$C_6H_5CH_2OCH_2Cl$	25 (12) or 90 (1.5)	~100/0 (~85)

[a] Percentages determined from NMR spectra. [b] The yields are based on β-keto ester reacted and are not optimized.

Scheme I[a]



[a] a, R = CH_2CH_3, G = K; b, R = HC $(CH_3)_2$, G = n-Bu_4; c, R = $CH_2CH{=}CH_2$; d, R = $CH_2OCH_2C_6H_5$

acyclic systems where by suitable control of conditions it has been possible to obtain high proportions of either C-alkylation (>90%)[3] or O-alkylation (>90%)[4,5] products. It is noteworthy that exclusive O-alkylation has been observed in the reaction of *both* cyclic and acyclic β-keto esters with (dimethylamino)ethyl chloride[6] and with methoxymethyl chloride;[7] however, alkylation of the ambident anions of cyclic β-keto esters with various other electrophiles normally results in C-alkylations.[8-10] We were interested to know how closely the behavior of cyclic β-keto esters would parallel that of their acyclic counterparts, and we report here our results on the O-alkylation of the enolate of 2-(carbomethoxy)cyclopentanone (**1**) under the conditions known to give predominant O-alkylation in the acyclic systems (Scheme I).

For maximization of the attack of the electrophile on the oxygen atom of the ambident anion **2**, the alkylations were conducted with the highly dissociated K^+ or n-Bu_4N^+ enolates in HMPA. In view of the generalization[15] that the orientation of attack is determined by the hardness or softness of the leaving group atom attached to carbon, the reactions were carried out with electrophiles embodying hard leaving groups, so as to further favor O-alkylation. The results are summarized in Table I.

The reaction of the potassio-2-(carbomethoxy)cyclopentanone **2a** with diethyl sulfate or ethyl p-toluenesulfonate (entries 1–3 in Table I)[16a] produced ~65% of O-alkylated product **3a** in addition to 35% of the C-alkylated **4a**. Thus, during ethylation of **1** somewhat lower amounts of O-alkylation products (~65%) are formed as compared to alkylation in the acyclic system, ethyl acetoacetate, where under similar conditions ~80–90% of β-ethoxycrotonate has been obtained. It is interesting, on the other hand, that the reaction of **2a** with triethyloxonium tetrafluoroborate (entry 4) gave an O-/C-alkylation ratio comparable with that of the acetoacetic ester:[4] 85% of O-alkylation product **3a** and 15% of **4a**. Treatment of **2a** with ethyl 2,4-dinitrobenzenesulfonate also gave (in low yield) O-alkylation product **3a** (O-/C-alkylation ratio of 80/20; entry 5). The reaction of **2a** with the bulkier isopropyltosylate afforded **3b** (75%; entry 6)[16b] and **4b** (25%). No significant increase in the proportion of O-alkylation was observed when the alkylation with isopropyl tosylate was carried out on the tetra-n-butylammonium enolate **2b** (O-/C-alkylation ratio of 80/20; entry 7). As anticipated reaction of **2a** with allyl chloride resulted in almost exclusive C-alkylation (O-/C-alkylation ratio of 10/90; entry 8).[16c]

Maximum O-alkylation could be obtained, as expected, by alkylation with (benzyloxy)methyl chloride which formed the O-alkylation product **3d** in very high isolated yield (~85%, entry 9).[16d] The exclusive formation of O-alkylation product with (benzyloxy)methyl chloride compared to other alkylating agents used is presumably due to the high degree of S_N1 character of this reaction.[3] With this chloro ether there appears to be no major difference in the extent of O-alkylation between the cyclic β-keto ester system and the acyclic counterpart.

Experimental Section

The general procedure for O-alkylation is as follows. 2-(Carbomethoxy)cyclopentanone (1, 1 mmol) in dry ether (2 mL) was treated with sublimed KO-t-Bu (1 mmol) under an argon atmosphere at ~20 °C for 15 min.[4] The solvent was distilled off, and the solid salt was dried at 70–75 °C under vacuum (~0.05 mm) for ~0.5 h. The salt was dissolved in dry HMPA (1 mL) at ambient temperature and treated with the electrophile for the times and at the temperatures indicated in Table I. The workup involved dilution with ~20 mL of pentane at room temperature, followed by washing the mixture with water and drying it over $MgSO_4$. After removal of the solvent the products were analyzed by NMR spectroscopy.[16]

Potassium enolates were also made by brief treatment of the β-keto ester 1 with KH (washed with pentane) directly in the HMPA reaction medium. The corresponding tetrabutylammonium enolate **2b** was generated in situ by exchange of the potassium enolate **2a** with n-$Bu_4N^+F^-$ or n-$Bu_4N^+O^-TS$.

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Registry No. 1, 10472-24-9; **2a**, 61114-30-5; **2b**, 74036-87-6; **3a**, 74036-88-7; **3b**, 74036-89-8; **3c**, 74036-90-1; **3d**, 74036-91-2; **4a**, 25684-00-8; **4b**, 74036-92-3; **4c**, 74036-93-4; $(C_2H_5O)_2SO_2$, 64-67-5; $C_2H_5OSO_2C_6H_4$-p-CH_3, 80-40-0; $(C_2H_5)_3O^+BF_4^-$, 368-39-8; $C_2H_5OSO_2C_6H_3$-2,4-$(NO_2)_2$, 3183-89-9; $(CH_3)_2CHOSO_2C_6H_4$-p-CH_3, 2307-69-9; $CH_2=CHCH_2Cl$, 107-05-1; $C_6H_5CH_2OCH_2Cl$, 3587-60-8.

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(16) Characteristic bands in the NMR (CCl_4): for **3a** δ 4.04 (q, 2 H, J = 7 Hz), 3.62 (s, 3 H), 1.35 (t, 3 H, J = 7 Hz); for **4a** δ 3.68 (s, 3 H), 0.87 (t, 3 H, J = 7 Hz); for **3b** δ 4.45 (septet, 1 H, J = 7 Hz), 3.6 (s, 3 H), 1.26 (d, 6 H, J = 7 Hz); for **4b** δ 3.66 (s, 3 H), 0.82 and 0.87 (two equal-intensity doublets, 6 H, J = 7 Hz). Identical spectral features are displayed by the isopropylation products prepared by the literature method:[10c] for **3c** δ 5.65 (m, 1 H), 5.08 (m, 2 H), 3.7 (s, 3 H); for **4c** δ 4.55 (m, 2 H), 3.63 (s, 3 H); for **4a** δ 7.28 (s, 5 H), 5.06 (s, 2 H), 4.67 (s, 2 H), 3.66 (s, 3 H), 2.55 (m, 4 H), 1.8 (m, 2 H); IR ($CHCl_3$) 1710, 1695, 1640 cm^{-1}; mass spectrum (CI), m/e 263 (M + 1).