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Use of the Thallium Trinitrate Catalyzed Rearrangement of Ketones in the Synthesis of an Acidic Morphinan Derivative

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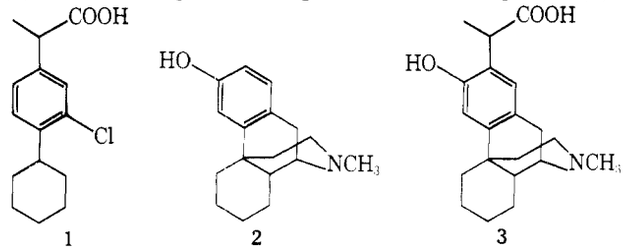
Received July 21, 1977

The introduction of the α-methylacetic acid side chain on D,L-*N*-methyl-3-hydroxymorphinan was carried out in an unsuccessful attempt to combine analgesic activity with the antiinflammatory activity associated with 2-arylpropionic acid derivatives. Using D,L-*N*-allyl-3-hydroxymorphinan as starting material, the key steps in the reaction sequence are the thallium trinitrate rearrangement of D,L-2-acetyl-3-methoxy-*N*-carboethoxymorphinan followed by the careful monomethylation of the acetic acid side chain of the rearrangement product using methyl iodide and lithium diisopropylamide. The Taylor–McKillop rearrangement is demonstrated to be useful in complex systems such as the morphinan.

In an attempt to combine both central analgesic and antiinflammatory activity in a single molecule we have developed a synthetic route to **3**, a molecule possessing both the structural features of the antiinflammatory phenylpropionic acids (**1**)[1] and the morphinan analgesics such as levorphanol (**2**).[2]



1 2 3

Results and Discussion

The synthetic plan envisaged introduction of the 2-propionic acid side chain on a suitable morphinan intermediate employing acylation, followed by rearrangement to the acid using the recently developed thallium trinitrate procedure of McKillop and Taylor.[3] Because there was insufficient information available on whether this reaction would proceed well with a propiophenone or with a free phenolic hydroxyl present, some initial model experiments were carried out. Direct rearrangement of propiophenone to methyl α-methylphenylacetate under the conditions of McKillop and Taylor gives poor yields.[3] Thallium trinitrate adsorbed on an insoluble inorganic support such as Florisil[4] or K-10[5] has been utilized to carry out this direct transformation. In our hands TTN adsorbed on Florisil led to none of the desired product and propiophenone was recovered quantitatively. The activity of this reagent was confirmed by reaction with acetophenone, which gave methyl phenylacetate in high yields. Therefore, instead of trying to sort out the reasons for such behavior with adsorbed thallium trinitrate, it proved more efficient to rely on direct methylation of the acetic acid side chain.

An attempted thallium-catalyzed rearrangement of *o*-hydroxyacetophenone (**5a**) at room temperature for 24 h gave no reaction, while the corresponding methyl ether (**5b**) was converted smoothly to the phenylacetate derivative **6b** in 15 min. Thus blocking of phenolic *o*-hydroxy groups is a requirement in the thallium trinitrate reaction.

As this rearrangement has been reported to proceed with difficulty with basic molecules[6] (presumably due to complex formation with the basic center), application of the thallium reaction to the morphinan system would be expected to require prior conversion of the amine to an acyl or carbamate derivative.

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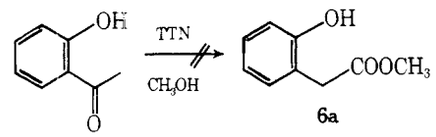
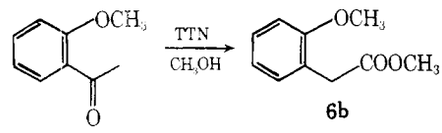


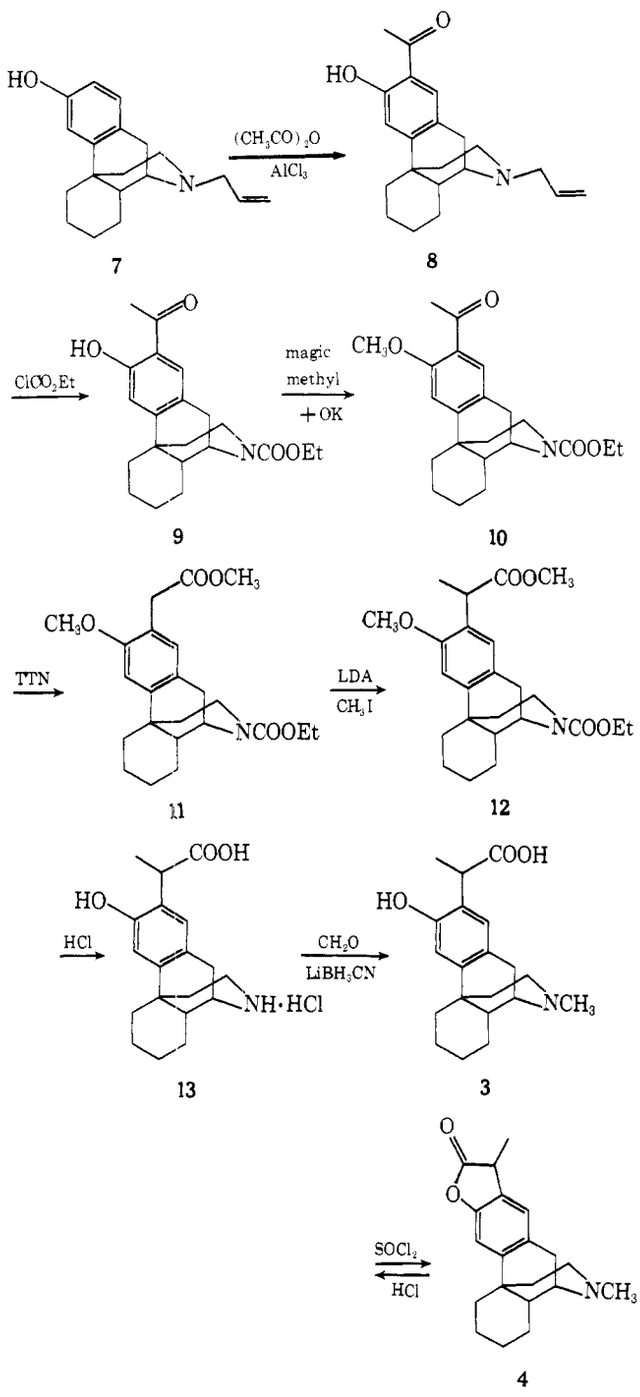
5a 6a



5b 6b

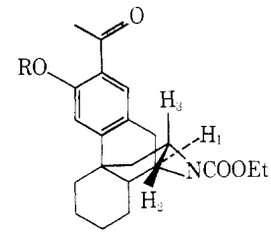
The plan of synthesis of **3** is outlined in Scheme I. D,L-3-Hydroxy-*N*-allylmorphinan (**7**) required as starting material was prepared according to the general procedure of Schnider and co-workers.[7]

Scheme I



Acetylation of **7** to give **8** employing acetic anhydride and aluminum chloride at 140 °C in nitrobenzene took place in 30 min exclusively at the 2 position. The position of acetylation was easily established from the two aromatic singlets at δ 7.03 and 7.67, demonstrating the para relationship of the two protons. The vigorous conditions required for acetylation were presumably a consequence of the presence of the basic nitrogen.[8]

Compound **8** was converted to **9** by reaction with ethyl chloroformate in refluxing benzene. The 220-MHz proton NMR spectrum of **9** indicated restricted rotation of the carboethoxy group as evidenced by the two broad singlets at δ 4.30 and 4.44 for equatorial H_1. The proton H_2, also deshielded as a consequence of lying in the carbonyl plane,[9] is seen as a pair of doublets centered at δ 3.88. The axial proton H_3 on the carbon α to the nitrogen showed an absorption of about δ 2.57 as several lines partially hidden by the acetyl group. Shielding was due to the proton being axial and over the π system of the benzene ring.[10]



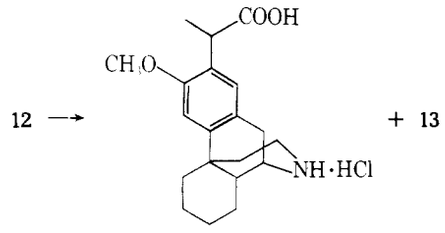
9

The potassium salt of **9**, generated by treatment with potassium *tert*-butoxide in glyme, was easily and quantitatively methylated with magic methyl (methyl fluorosulfonate)[11] at room temperature within 5 min to give **10**. Again with **10**, the 220-MHz NMR spectrum showed evidence of restricted rotation of the carbamate group as the equatorial α protons lying in the plane of the carbonyl are at δ 4.35 and 3.84 as broad signals. This indicates that the ambient temperature is essentially the coalescence temperature.

Thallium trinitrate rearrangement occurred smoothly on this ketone with the transformation **10** to **11** completed within 30 min at room temperature. The structure of **11** was proven by analysis, mass spectrometry, and NMR, which showed the expected methylene singlet at δ 3.40. Restricted rotation was again observed with two broad and poorly resolved absorptions at δ 4.38 and 4.23 for the proton H_1 and δ 3.90 and 3.81 for proton H_2.

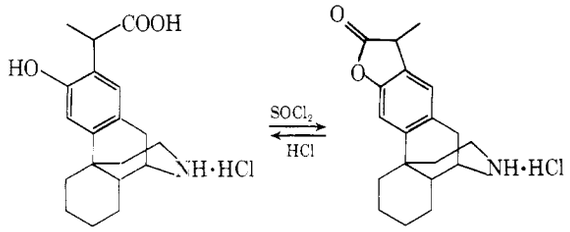
The C-alkylation of **11** was carried out using lithium diisopropylamide in tetrahydrofuran at −70 °C according to the procedure of Rathke,[12] in which the anion is quenched with excess methyl iodide. With careful precautions to exclude moisture, it was possible to obtain **12** with <1% of either starting material **9** or dialkylated ester. It was essential that the reaction be monitored by mass spectrometry in order to determine the exact quantity of base to be used.

The complete hydrolysis of **12** to **13** in acid proved to be a very slow reaction. The ester functionality disappeared first, followed by much slower hydrolysis of the carbamate function. After 3 days of refluxing **12** in equal volumes of concentrated hydrochloric acid and acetic acid, it was possible to detect and isolate the corresponding methoxy derivative **14**. After 144 h of reflux, the removal of the methoxyl group was completed. The resulting solution contained a mixture of the hydroxy acid **13** and its corresponding lactone **15**, easily detected by its infrared carbonyl at 1820 cm^{-1}. Treatment with chloroform afforded a clean separation of the lactone **15** from the hydroxy acid **13**. Heating the lactone in dilute hydrochloric acid solution and repeating the chloroform treatment eventually afforded a high yield of the hydrochloride salt of **13**. Further



14

examination of this equilibrium demonstrated that heating with thionyl chloride afforded a clean conversion of **13** to **15.**



13 15

The N-methylation of **13** to **3** was accomplished with the conditions of Borsch and collaborators[13] using formaldehyde and sodium cyanoborohydride in acetonitrile. Again, there was an equilibrium between the acid form **3** and the lactone **4.**

Biological testing on both **3** and **4** revealed neither analgesic nor antiinflammatory activity.

Experimental Section

Melting points were taken on a Thomas Hoover apparatus and are uncorrected. Infrared spectra were determined on a Perkin-Elmer 257 grating spectrophotometer. A Varian EM-360 instrument was used to record NMR spectra in deuteriochloroform using tetramethylsilane as an internal standard. Elemental analyses were carried out by Dr. C. Daessle, Organic Microanalyses. The low-resolution mass spectral analyses were performed by Morgan-Schaffer Corp. and the high-resolution mass spectral analyses were performed on an AE1 MS 902 mass spectrometer. The 220-MHz NMR spectra were carried out by the Canadian 220-MHz NMR Centre.

All reactions as well as column chromatography were followed by TLC using precoated 0.25-mm silica gel plates (Eastman Kodak) with visualization of spot either by UV or by exposure to iodine vapors.

Methyl Phenylacetate. To acetophenone (120 mg, 1 mmol) in carbon tetrachloride (5 mL) was added 1.5 g of thallium trinitrate adsorbed on Florisil prepared by adding 4.5 g of thallium trinitrate dissolved in 5 mL of methanol and 5 mL of methyl orthoformate to 10 g of Florisil and evaporating under vacuum to constant weight. The mixture was stirred at room temperature for 20 h. The spent reagent was removed by filtration, the filtrate was washed with water, dried, and evaporated under vacuum to an oil, identical with authentic methyl phenylacetate by Ir.[14]

Under identical conditions, propiophenone (135 mg, 1 mmol) was recovered intact after 20 h of reaction.

Methyl *o*-Methoxyphenylacetate (6b). *o*-Methoxyacetophenone (150 mg, 1 mmol) was added to 2.5 mL of methanol and 0.5 mL of 70% perchloric acid. It was cooled to 0 °C with an ice bath and thallium trinitrate (500 mL, 1.13 mmol) was added. It was stirred and when it reached room temperature, the reaction mixture was poured onto water and extracted with methylene chloride, washed with water, and dried over sodium sulfate. The residue was distilled under vacuum to yield 102 mg (60%) of methyl *o*-methoxyphenylacetate: bp 120 °C (20 mm); IR: 1750 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) δ 3.61 (2 H, s, CH_2), 3.66 (3 H, s, CH_3), 3.81 (3 H, s, CH_3), 7.00 (4 H, m, aromatic).

Anal. Calcd for $C_{10}H_{12}O_3$: C, 66.67; H, 6.71. Found: C, 66.20; H, 6.50.

The use of identical conditions on *o*-hydroxyacetophenone left it unchanged after 24 h at room temperature.

D,L-*N*-Allyl-3-hydroxymorphinan (7). D,L-*N*-Allyl-3-hydroxymorphinan (**7**) was prepared essentially by the method of Schnider and Hellerbach with an overall yield of 21% from cyclohexenylacetonitrile: mp 184–186 °C (lit.[7] 177–179.5 °C).

D,L-*N*-Allyl-2-acetyl-3-hydroxymorphinan (8). D,L-*N*-Allyl-3-hydroxymorphinan (6.7 g, 23.7 mmol), aluminium chloride (31 g, 0.23 mol), and acetic anhydride (7.5 mL) in 120 mL of nitrobenzene were heated under nitrogen for 30 min. Water was added and the nitrobenzene was removed by steam distillation. The aqueous solution was made basic with ammonium hydroxide and extracted three times with ethyl acetate. The extract was washed with water and dried (Na_2SO_4). Evaporation under vacuum left D,L-*N*-allyl-2-acetyl-3-hydroxymorphinan as a yellow oil (5.7 g, 74%): homogeneous by TLC, R_f 0.5 (ethyl acetate); IR 1655 (C=O), 1630 cm^{-1} (C=C); ^1H NMR ($CDCl_3$) δ 2.67 (3 H, s, CH_3), 7.03 (1 H, s, H_4), 7.67 (1 H, s, H_1); MS M^+ 325; hydrochloride salt mp 280–283 °C dec.

Anal. Calcd for $C_{21}H_{27}NO_2 \cdot HCl$: C, 69.69; H, 7.80; N, 3.87; Cl, 9.80. Found: C, 70.11; H, 8.00; N, 3.75; Cl, 9.80.

D,L-*N*-Carboethoxy-2-acetyl-3-hydroxymorphinan (9). D,L-*N*-Allyl-2-acetyl-3-hydroxymorphinan (6.7 g, 20.6 mmol) in 65 mL of benzene was treated with 65 mL of freshly distilled ethyl chloroformate. Reflux was maintained for 13 h after which the volatiles were removed under vacuum. The solid residue was dissolved in 300 mL of methylene chloride; the solution was washed with dilute hydrochloric acid and with water, dried (Na_2SO_4), and concentrated under vacuum. The residual oil was triturated in ether. The solid *N*-carboethoxy-2-acetyl-3-hydroxymorphinan (5.4 g, 74%) was filtered and air dried: mp 176–178.5 °C; it was homogeneous by TLC, R_f 0.8 (2% methanol in chloroform); IR 1710 and 1665 cm^{-1} (C=O); NMR ($CDCl_3$) δ 1.25 (3 H, t, J = 7 Hz, CH_3), 2.60 (3 H, s, CH_3CO), 4.13 (2 H, q, J = 7 Hz, CH_2), 6.90 (1 H, s, H_4), 7.43 (1 H, s, H_1); MS M^+ 357.

Anal. Calcd for $C_{21}H_{27}NO_4$: C, 70.56; H, 7.61; N, 3.92. Found: C, 69.95; H, 7.56; N, 4.02.

D,L-*N*-Carboethoxy-2-acetyl-3-methoxymorphinan (10). To D,L-*N*-carboethoxy-2-acetyl-3-hydroxymorphinan (1.79 g, 5.0 mmol) in 50 mL of dimethoxyethane was added potassium *tert*-butoxide (0.85 g, 7.5 mmol) and then methyl fluorosulfonate (0.57 g, 5 mmol). Stirring was maintained for 15 min at room temperature. The reaction was quenched with water and then extracted with ether. The ether extract was washed with water and dried (Na_2SO_4). Evaporation yielded D,L-*N*-carboethoxy-2-acetyl-3-methoxymorphinan as an oil that crystallized on standing (1.8 g, 98%): mp 100–100.5 °C; it was homogeneous by TLC, R_f 0.6 (chloroform–petroleum ether, 1:1 v/v); IR 1715 and 1685 cm^{-1} (C=O); NMR ($CDCl_3$); δ 1.25 (3 H, t, J = 7 Hz, CH_2), 2.63 (3 H, s, CH_3CO), 3.90 (3 H, s, CH_3), 4.20 (2 H, q, J = 7 Hz, CH_2), 6.90 (1 H, s, H_4), 7.52 (1 H, s, H_1); MS M^+ 371.

Anal. Calcd for $C_{22}H_2NO_4$: C, 71.13; H, 7.87; N, 3.77. Found: C, 70.74; H, 8.05; N, 3.65.

D,L-*N*-Carboethoxy-2-carbomethoxymethyl-3-methoxymorphinan (11). D,L-*N*-Carboethoxy-2-acetyl-3-methoxymorphinan (2.9 g, 7.9 mmol) was dissolved in 50 mL of methanol. The solution was cooled and 9.2 mL of 70% perchloric acid was added slowly. Thallium trinitrate hydrate (7.0 g, 15.9 mmol) was then added. Within 5 min, a precipitate of thallous nitrate appeared. The suspension was stirred at room temperature for 45 min and then poured onto water. Following extraction with chloroform, drying over sodium sulfate, and evaporation, D,L-*N*-carboethoxy-2-carbomethoxymethyl-3-methoxymorphinan was obtained as an oil that crystallized on standing: mp 94.5–95 °C; homogeneous by TLC, R_f 0.8 in chloroform–petroleum ether, 1:1 v/v; IR 1755 and 1705 cm^{-1} (C=O); NMR ($CDCl_3$) δ 1.25 (3 H, t, J = 7 Hz, CH_3), 3.63 (2 H, s, CH_2), 3.75 (3 H, s, CH_3OCO), 3.85 (3 H, s, CH_3O), 6.85 (1 H, s, H_4), 7.00 (1 H, s, H_1).

Anal. Calcd for $C_{23}H_{31}NO_5$: C, 68.80; H, 7.78; N, 3.49. Found: C, 68.86; H, 8.22; N, 3.70.

D,L-*N*-Carboethoxy-2-(1-carbomethoxyethyl)-3-methoxymorphinan (12). D,L-*N*-Carboethoxy-2-carbomethoxymethyl)-3-methoxymorphinan (7.8 g, 19.4 mmol) in 40 mL of anhydrous tetrahydrofuran was added slowly to a solution of lithium diisopropylamide (2.08 g, 19.4 mmol) in 35 mL of tetrahydrofuran maintained at −75 °C. The mixture was stirred for 10 min then quenched by the addition of 20 mL of methyl iodide. The reaction was stirred for 20 minutes while the temperature was allowed to increase to room temperature. Water was added and the resulting mixture extracted twice with ether. The ether extract was washed with water, dried over sodium sulfate, and evaporated to yield 8.04 g (100%) of D,L-*N*-carboethoxy-2-(carbomethoxyethyl)-3-methoxymorphinan as an oil which solidified to an amorphous solid, homogeneous by TLC; R_f 0.5 in methylene chloride. Mass analysis revealed the product to be a mixture with the relative heights of apparent ions being 1.3% for starting material, 98.2% for monomethyl substituted, and 0.5% for dimethyl substituted: IR 1760 and 1705 cm^{-1} (C=O); NMR δ 1.27 (3 H, t, J = 7 Hz, CH_3), 1.43 (3 H, d, J = 7 Hz, CH_3), 3.67 (3 H, s, CH_3OCO), 3.80 (3 H, s, CH_3O), 4.13 (2 H, q, J = 7 Hz, CH_2), 6.77 (1 H, s, H_4), 6.93 (1 H, s, H_1).

Anal. Calcd for $C_{24}H_{33}NO_5$: C, 69.37; H, 8.00; N, 3.37. Found: C, 69.55; H, 7.77; N, 3.27.

D,L-2-(1-Carboxyethyl)-3-hydroxymorphinan Hydrochloride (13). D,L-*N*-Carboethoxy-2-carbomethoxyethyl-3-methoxymorphinan (4.1 g, 9.9 mmol) in 100 mL of acetic acid and 100 mL of concentrated hydrochloric acid was refluxed for a period of 6 days under a nitrogen atmosphere. The reaction mixture was evaporated and the residue treated with 60 mL of chloroform. The solid that crystallized was filtered, washed with chloroform, and air dried. The filtrate was evaporate to dryness and the residue heated with 20 mL of 1 N hydrochloric acid on a steam bath for 30 min. Following evaporation to dryness and repeat treatment a second crop of crystals was obtained. The two crops were combined to yield 2.5 g (74%) of D,L-2-(1-carboxyethyl)-3-hydroxymorphinan hydrochloride: mp 216–225 °C dec; IR 1730 cm^{-1} (C=O); NMR (D_2O) δ 1.45 (3 H, d, J = 7 Hz, CH_3), 6.97 (1 H, s, H_4), 7.15 (1 H, s, H_1); MS M^+ 315.

Anal. Calcd for $C_{19}H_{25}NO_3$·HCl: C, 64.85; H, 7.45; N, 3.98; Cl, 10.08. Found: C, 64.65; H, 7.34; N, 3.74; Cl, 10.04.

D,L-*N*-Methyl-2-(1-carboxyethyl)-3-hydroxymorphinan (3). To D,L-2-(1-carboxyethyl)-3-hydroxymorphinan hydrochloride (2.5 g, 7.1 mmol) suspended in 25 mL of acetonitrile was added 3.0 mL of 36% aqueous formaldehyde. After stirring 5 min, addition of sodium cyanoborohydride (2.0 g, 32 mmol) was made. Complete solution occurred, but within 5 min, an oily black material was observed. Stirring was continued for 45 min while acetic acid was added to maintain a pH of 6–7. The reaction mixture was taken to dryness and the black residue suspended in 100 mL of chloroform. The mixture was treated with 5 mL of thionyl chloride under reflux for 30 min and then filtered. The residue was washed well with chloroform and the filtrate was evaporated to yield 2.2 g (84%) of the lactone of D,L-*N*-methyl-2-(1-carboxyethyl)-3-hydroxymorphinan hydrochloride. This solid was suspended in 50 mL of 1 N hydrochloric acid and refluxed for 1 h. The solution was passed through a column of Dowex 50, H^+ charged. Elution with ammonium hydroxide (1.5 N) yielded 1.2 g of D,L-*N*-methyl-2-(1-carboxyethyl)-3-hydroxymorphinan: mp 237–239 °C; homogeneous by TLC, R_f 0.8 in methanol–chloroform–concentrated ammonia, 4:8:0.5 v/v/v; IR 1570 cm^{-1} (C=O); NMR (D_2O) δ 1.35 (3 H, d, J = 7 Hz, CH_3), 2.90 (3 H, s, CH_3N), 6.97 (1 H, s, H_4), 7.17 (1 H, s, H_1); MS $M^+ - H_2O$ 311; no M^+ detected.

Anal. Calcd for $C_{20}H_{27}NO_3$: C, 72.92; H, 8.26; N, 4.25. Found: C, 72.71; H, 8.65; N, 4.40.

Lactone of D,L-*N*-Methyl-2-(1-carboxyethyl)-3-hydroxymorphinan Oxalate Salt (4). Crude lactone of D,L-*N*-methyl-2-carboxyethyl-3-hydroxymorphinan hydrochloride (1.0 g, 3.04 mmol) suspended in ether was carefully neutralized with dilute ammonium hydroxide. The ether layer was washed with water, dried over sodium sulfate, and concentrated to yield 0.64 g of the free lactone as an oil. This was dissolved in 25 mL of isopropyl alcohol and a solution of oxalic acid in isopropyl alcohol (180 mg, 2 mmol in 1 mL) was added. The oxalate salt which slowly crystallized overnight was filtered to yield 520 mg of salt; mp 162 °C dec; IR 1810 cm^{-1} (C=O); NMR ($CDCl_3$) (on free base) δ 1.57 (3 H, d, J = 7 Hz, CH_3), 2.43 (3 H, s, CH_3N), 7.00 (1 H, s, H_4), 7.27 (1 H, s, H_1); MS M^+ 311.

Anal. Calcd for $C_{20}H_{25}NO_2 \cdot C_2H_2O_4$: C, 65.10; H, 6.50; N, 3.61. Found: C, 64.89; H, 6.84; N, 3.89.

Acknowledgments. The authors would like to extend their appreciation to Mr. R. E. Rhodes for recording the high resolution mass spectra and to Mr. J. Scheigetz for preparing the *N*-allyl-3-hydroxymorphinan. The authors express their thanks to Drs. Alan W. Douglas and E. W. Tristram for helpful comments and suggestions on this manuscript. The authors wish also to thank Dr. K. T. Liu, Princeton University, for a helpful discussion on the preparation and use of TTN adsorbed on Florisil.

Registry No.—**3,** 64739-24-8; **4,** 64739-25-9; **4** HCl, 64739-26-0; **4** oxalate, 64739-27-1; **6b,** 27798-60-3; **7,** 64783-66-0; **8,** 64739-28-2; **8** HCl, 64739-29-3; **9,** 64739-30-6; **10,** 64739-31-7; **11,** 64739-32-8; **12,** 64739-33-9; **13,** 64739-34-0; methyl phenylacetate, 101-41-7; acetophenone, 98-86-2; methyl orthoformate, 149-73-5; *o*-methoxyacetophenone, 579-74-8; methanol, 67-56-1; acetic anhydride, 108-24-7; ethyl chloroformate, 541-41-3; methyl fluorosulfonate, 421-20-5; methyl iodide, 74-88-4; formaldehyde, 50-00-0; TTN, 13746-98-0.

References and Notes

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