The Preparation and Synthetic Utility of O-Substituted Normethylmorphines

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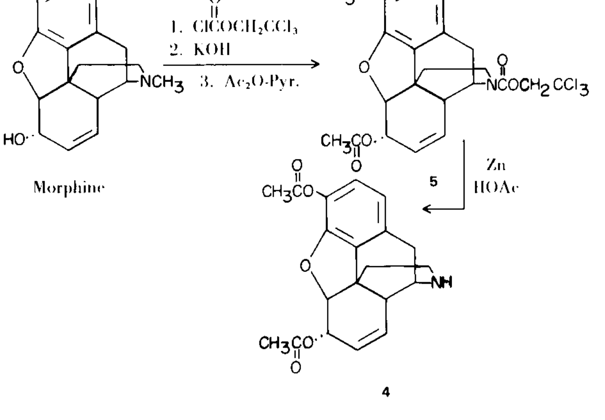
Previously described alkylation procedures on normethylmorphine in ethanol usually give low yields of *N*- and (phenolic) *O,N*-alkylated products. While the *O*-alkylation problem has been overcome for alkyl halides by doing the alkylations in dimethylformamide, reactive halides such as ethyl bromoacetate still give some *O*-alkylation. Selective *N*-acylation on normethylmorphine would present even more difficulty. We have developed syntheses of two phenolic *O*-substituted normethylmorphines which allow selective reaction on nitrogen. 3,6-Diacetylnormethylmorphine (normethylheroin) is prepared *via* the recently described trichloroethyl chloroformate method of Montzka *et al.* as applied to heroin. The reaction of *N,N*-diethylcarbamoyl chloride on morphine gives 3-(*N,N*-diethylcarbamoyl)morphine, *i.e.* the phenolic hydroxyl is derivatized. Its 6-acetyl derivative is *N*-demethylated by the von Braun (cyanogen bromide) method to give 3-(*N,N*-diethylcarbamoyl)normethylmorphine. Norheroin is monoalkylated in good yield on nitrogen with ethyl bromoacetate in dimethylformamide. It is similarly *N*-acylated with chloroacetyl chloride in methylene chloride.

We have sought to prepare *O,O*-disubstituted or C-3 (phenolic) *O*-substituted normethylmorphines. Such compounds should be useful for selective alkylation or acylation on nitrogen. Few such compounds have been available to date. One exception is the briefly described 3,6-di(trimethylsilyl)normethylmorphine (**1**) (1). We have repeated the preparation of **1** directly from normethylmorphine but are uncertain of its synthetic utility because of the lability of the TMS groups.

Our need for normethylmorphine derivatives with a blocked phenolic (C-3) hydroxyl was increased when we found that alkylation of normethylmorphine (**2**) with various reagents including ethyl bromoacetate in propanol gave mixtures including *N*-alkylated and C-3 *O,N*-dialkylated products (2,3). Although some recent alkylations of **2** in dimethylformamide give *N*-alkylation (in low yield, 4) we decided to protect the C-3 hydroxyl.

The *N*-demethylation of tertiary methylamines has been done classically with cyanogen bromide, the von Braun reaction (5). Application of this method to the synthesis of 3,6-diacetylnormethylmorphine (norheroin, **4**) leads to the hydrolysis of the acetate groups so that normethylmorphine (**2**) is obtained. The use of phenyl chloroformate (6a) involves milder conditions but the basic hydrolytic workup again removes the acetoxy groups. The recent modified workup using aqueous hydrazine (6b) should also hydrolyze the *O*-acetates. Ethyl chloroformate does not work on morphine (6a). The use of diethyl azodicarboxylate represents an even milder *N*-demethylation of morphine or heroin but the latter gives 6-acetoxynormethylmorphine (**3**, 7a). Thus all of these *N*-demethylation methods involve acidic or basic hydrolysis of *N*-nitriles or carbamates with concomitant loss of at least the phenolic (C-3) acetate.

We have utilized the recently described 2,2,2-trichloroethyl chloroformate method of Montzka, *et al.*, (8) in a solution to this problem. The cleavage of *N*-(2′,2′,2′-trichloroethylcarbamoyl)-3,6-diacetylmorphine (5) with zinc and acetic acid gives **4** in 58% overall yield from morphine.



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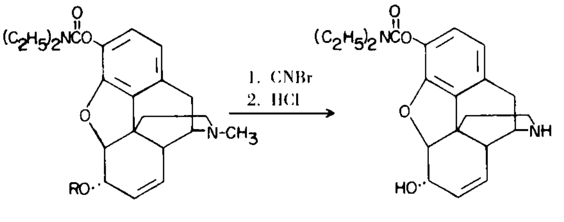
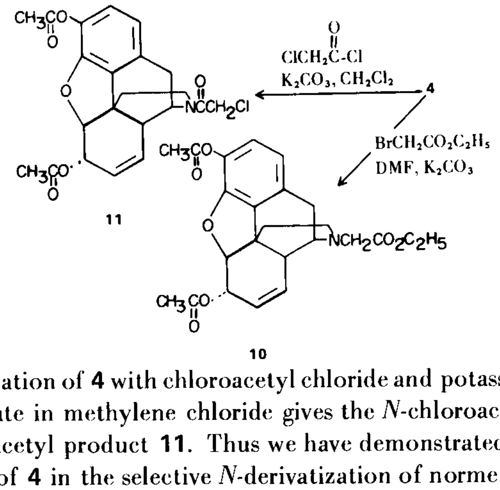
A successful alternate synthesis of a C-3 O-substituted normethylmorphine has involved the diethylcarbamoyl group, previously shown by Bartels-Keith to survive the acidic hydrolysis step of the von Braun degradation of dihydromorphinone (9). Reaction of morphine with N,N-diethylcarbamoyl chloride gives 3-diethylcarbamoylmorphine (**6**). Acylation was shown to occur on the phenolic hydroxyl by the absence of a shift in the ultraviolet spectrum of **6** when treated with base. Acetylation of **6** gave the 6-acetoxy **7**. Reaction of **7** with cyanogen bromide gives the cyano compound **8** which is hydrolyzed with dilute hydrochloric acid to give 3-(N,N-diethylcarbamoyl)-normethylmorphine (**9**).



6 R = H
7 R = $COCH_3$
9

Since the 6-hydroxyl group is not readily alkylated, we believe that the preparation of **9** represents another solution to the problem of avoiding (phenolic) O-alkylation in the morphine series. The phenolic hydroxyl is also preferentially acylated with diphenylcarbamoyl chloride (see Experimental Section) so that such acylations are hopefully general.

The alkylation of norheroin (**4**) in dimethylformamide with ethyl bromoacetate (and potassium carbonate to remove hydrogen bromide) gives the N-alkylated product **10** in 78% yield with the acetoxy groups intact.



11

10

Acylation of **4** with chloroacetyl chloride and potassium carbonate in methylene chloride gives the N-chloroacetyl-O,O-diacetyl product **11**. Thus we have demonstrated the utility of **4** in the selective N-derivatization of normethylmorphine.

EXPERIMENTAL

All solvents were dried by distillation from calcium hydride, phosphorus pentoxide, or lithium aluminum hydride. Most reactions were conducted under protection from the atmosphere by a calcium chloride drying tube or under nitrogen (as indicated). Organic solutions were dried over anhydrous magnesium sulfate. Infrared spectra were recorded on Perkin-Elmer 457 and 700 infrared spectrophotometers. Ultraviolet spectra were recorded on a Perkin-Elmer 402 spectrophotometer. Microanalyses were performed by Galbraith Laboratories, Knoxville, Tenn. Nmr spectra were recorded on a Varian A-60A spectrometer with TMS as an internal standard. Mass spectra were recorded on a DuPont CEC 21-492 mass spectrometer. Melting points were taken on Mel-Temp and Thomas-Hoover "Uni-Melt" apparatus and are uncorrected. Thin layer chromatograms were done with Eastman Kodak silica plates using chloroform as solvent. For amines, some ammonia and ethanol were added to avoid streaking. The nmr spectra of the morphine derivatives all show the aromatic protons as an AB quartet. Approximate values of the A and B centers are δ 6.7-6.8 (C-1 proton) and 6.5-6.6 (C-2 proton, 10). Other protons include δ 5.7 (C-7 vinyl H), 5.4 (C-8 vinyl H), 5.1 (C-5, 6H), 2.21-2.25 (C-3 O-acetyl) and 2.10 (C-6 O-acetyl). Infrared and nmr spectra were consistent with the proposed structures. Pertinent values only are mentioned below.

N-(2′,2′,2′-Trichloroethylcarbamoyl)-N-normethylmorphine (**5a**).

A mixture of morphine (2.5 g., 0.0087 mole), sodium bicarbonate (15 g., 0.13 mole), and 2,2,2-trichloroethyl chloroformate (16 g., 0.078 mole) in chloroform (250 ml.) was heated at reflux for 60 hours. Water (100 ml.) was added, the organic layer was separated, washed, dried, and evaporated to give a residue which was dissolved in methanol (150 ml.) and treated with an aqueous solution of potassium hydroxide (5.6 g., 0.1 mole) and sodium bicarbonate (9.5 g., 0.11 mole) overnight with stirring. Acidification with hydrochloric acid, partial evaporation, and extraction with diethyl ether gave an oil which slowly crystallized. Recrystallization from ethyl acetate-petroleum ether gave **7** (3.3 g., 0.0074 mole, 85%), m.p. 189-191°, [lit. (8) 196-198°] (recrystallized from ether).

N-(2′,2′,2′-Trichloroethylcarbamoyl)-N-normethyl-3,6-diacetylmorphine (**5**).

Reaction of **5a** (3.25 g., 0.0073 mole) with acetic anhydride (30 ml.) and pyridine (8 ml.) gave **5** (3.7 g., 0.0070 mole, 96%), m.p. 142-142.5°; ir (Nujol): 1755, 1730, 1702 cm^{-1}; nmr (CCl_4): δ 4.75 (s, 2, CH_2CCl_3).

Anal. Calcd. for $C_{23}H_{22}Cl_3NO_7$: C, 52.05; H, 4.18; N, 2.64. Found: C, 52.07; H, 4.06; N, 2.53.

3,6-Diacetylnormethylmorphine (**4**).

The trichloroethylcarbamate **5** (0.53 g., 0.001 mole) was heated at reflux in acetic acid (10 ml.) with zinc (0.25 g.) for 30 minutes. The solvent was evaporated and the residue quickly partitioned between ethyl acetate and 2N-ammonium hydroxide. The organic layer was washed with water, dried, and evaporated *in vacuo* to give an oil which was (mainly) dissolved in diethyl ether and crystallized to give **4** (0.255 g., 0.00072 mole, 72%), m.p. 137-138°; ir (Nujol): 3340 (NH, sharp), 1735, 1760 cm^{-1}; nmr (deuteriochloroform): δ 2.25 (s, 3, C-3 $OCOCH_3$), 2.12 (s, 3, C-6 $OCOCH_3$).

Anal. Calcd. for $C_{20}H_{21}NO_5$: C, 67.59; H, 5.96; N, 3.94. Found: C, 67.80; H, 6.12; N, 3.78.

3-(N,N-Diethylcarbamoyl)morphine (**6**).

Reaction of morphine (2.00 g., 0.00704 mole) with diethyl carbamoyl chloride (1.0 g., 0.0074 mole) and pyridine (18 ml.) under nitrogen at reflux for 45 minutes, evaporation of the solvent *in vacuo* gave a residue which was dissolved in water (10 ml.), made basic with 2*N*-ammonium hydroxide, and kept at 0° for 1 hour. A precipitate was filtered and recrystallized from ethanol-water to give **6** (2.37 g., 0.00617 mole, 88%), m.p. 165-167°; ir (Nujol): 3440 (OH), 1695 cm^{-1}; nmr (deuteriochloroform): δ 3.40 (m, 4, CH_2CH_3), 2.43 (s, 3, NCH_3), 1.22 (t, 6, CH_2CH_3); uv max (95% ethanol) 275 sh, 281 nm (no change with sodium hydroxide, 11).

Anal. Calcd. for $C_{22}H_{28}N_2O_4$: C, 68.73; H, 7.34; N, 7.29. Found: C, 68.51; H, 7.32; N, 7.33.

3-(*N*,*N*-Diethylcarbamoyl)-6-acetylmorphine (**7**).

Reaction of **6** (2.37 g., 0.00617 mole) with acetic anhydride (15 ml.) and pyridine (5 ml.) under nitrogen on a steam bath for 2 hours, removal of solvents *in vacuo* gave a residue which was dissolved in water (15 ml.). The solution was made basic by the slow addition of 2*N*-ammonium hydroxide with stirring. A white precipitate formed and was filtered after 1 hour at 0°. Recrystallization from diethyl ether-petroleum ether gave **7** (2.2 g., 0.0052 mole, 84%), m.p. 115-116°; ir (Nujol): 1728 sh, 1720 cm^{-1}; nmr (deuteriochloroform): δ 3.42 (quart, 4, NCH_2CH_3), 2.43 (s, 3, NCH_3), 2.08 (s, 3, C-6 $OCOCH_3$), 1.23 (t, 6, NCH_2CH_3).

Anal. Calcd. for $C_{24}H_{30}N_2O_5$: C, 67.58; H, 7.09; N, 6.57. Found: C, 67.72; H, 7.21; N, 6.54.

3-(*N*,*N*-Diethylcarbamoyl)normethylmorphine (**9**).

A solution of **7** (0.400 g., 0.00094 mole) and cyanogen bromide (0.200 g., 0.0019 mole) in chloroform (20 ml.) was heated at reflux for 1.5 hours. After evaporation of the solvent *in vacuo*, the residue was dissolved in ethyl acetate. The solution was filtered, concentrated to 10 ml. and petroleum ether was added to crystallize *N*-cyano-3-(*N*,*N*-diethylcarbamoyl)-6-acetylnormethylmorphine (**8**, 0.340 g., 0.00078 mole, 83%), m.p. 214-214.5°; ir (Nujol): 2230 (CN), 1735 sh, 1720 cm^{-1}; nmr (deuteriochloroform): δ 3.45 (quart, 4, NCH_2CH_3), 2.2 (s, 3, C-6 $OCOCH_3$), 1.25 (t, 6, NCH_2CH_3).

Anal. Calcd. for $C_{24}H_{27}N_3O_5$: C, 65.89; H, 6.22; N, 9.61. Found: C, 65.78; H, 6.37; N, 9.52.

A solution of **8** (1.0 g., 0.0023 mole) in 1.67 *N*-hydrochloric acid (20 ml.) was heated at reflux under nitrogen for 20 hours, cooled, filtered and evaporated to give a residue which was dissolved in water (8 ml.) and cooled. After 6 hours at 0°, the resultant precipitate was filtered, and dissolved in water (8 ml.) to give a solution which was made basic with 2*N*-ammonium hydroxide. The resultant supernatent liquid was removed to leave a residue which was dissolved in ethanol (3 ml.) and then water (20 ml.) to give a cream-colored precipitate (*ca.* 0.060 g.). The mother liquors were extracted with chloroform (2 x 30 ml.) and the organic extracts and solid were combined, washed with water, dried, and evaporated *in vacuo* to give a residue which was recrystallized from ethyl acetate-petroleum ether to give **9** as white crystals (0.195 g., 0.00053 mole, 23%), m.p. 138-140°; nmr (deuteriochloroform): δ 3.42 (quart, 6 inc. NCH_2CH_3), 1.25 (t, 6, NCH_2CH_3); mass spectrum: (70 eV) m/e 370 ($M^{\dagger}$); ir (Nujol): 3418, 3470, 3320, 1685, 1708 cm^{-1}.

Anal. Calcd. for $C_{21}H_{26}N_2O_4$: C, 68.09; H, 7.07; N, 7.56. Found: C, 67.98; H, 7.18; N, 7.42.

3-(*N*,*N*-Diphenylcarbamoyl)morphine (**12**).

A mixture of morphine (1.0 g., 0.0035 mole) and diphenylcarbamoyl chloride (2.5 g., 0.0108 mole) in pyridine (20 ml.) was kept at reflux under nitrogen for 6 hours, and at 5° for 5 hours. Crystalline amine hydrochloride (1.6 g.) was filtered, dissolved in 9:1 water-methanol which was made basic with 2*N*-sodium hydroxide. After 1 hour at 0°, a precipitate was filtered and recrystallized from: (a) ethanol, (b) diethyl ether (2x) to give **12** (1.2 g., 0.0025 mole, 71%), m.p. 146-147°; ir (Nujol): 3420, 3480, 1715, 1670 (w) cm^{-1}; uv max (95% ethanol): 276, 280 sh nm (no change with sodium hydroxide 11); nmr (deuteriochloroform): δ 7.42 (br s, 10, phenyl H), 2.42 (s, 3, NCH_3).

Anal. Calcd. for $C_{30}H_{28}N_2O_4$: C, 74.98; H, 5.87; N, 5.83. Found: C, 74.77; H, 5.87; N, 5.78.

3,6-Di(Trimethylsilyl)normethylmorphine (**1**).

Normethylmorphine (**2**, 0.2 g., 0.00073 mole, 5) in dry DMF (2 ml.) was treated with hexamethyldisilazane (HMDS, 0.2 ml.) to liberate ammonia. After 16 hours at 25°, the solution was partially evaporated *in vacuo* to remove excess HMDS. An alternate procedure was followed in chloroform at reflux for 5 hours. Complete removal of solvents gave crude **1** which gave: ir (Nujol): 3305, 1080 (O Si-CH_3), 920, 970 (O-Si-Ar) cm^{-1}; nmr (deuteriochloroform): δ 0.17 (s, 9, C-6 OTMS), 0.22 (s, 9, C-3 OTMS); mass spectrum: (70 eV) m/e 415 ($M^{\dagger}$).

N-Carbethoxymethyl-3,6-diacetylnormethylmorphine (**10**).

A mixture of norheroin (**4**, 0.177 g., 0.0005 mole), anhydrous potassium carbonate (0.130 g., 0.00095 mole) and ethyl bromoacetate (0.085 g., 0.00051 mole) was heated at 110° under nitrogen in DMF (10 ml.) for 90 minutes. To the cooled solution, ethyl acetate and water (50 ml. each) were added; the organic layer was washed with water (2x), saturated sodium chloride, dried, and evaporated *in vacuo* to give a residue which was crystallized from diethyl ether-petroleum ether to give **10** (0.170 g., 0.00039 mole, 78%), m.p. 115-121°; ir (Nujol): 1755, 1745, 1725 cm^{-1}; nmr (deuteriochloroform): δ 4.22 (quart, 2, CH_2CH_3), 3.38 (s, 2, $CH_2C{=}O$), 1.28 (t, 3, CH_3CH_2). Further recrystallization gave m.p. 123-125°.

Anal. Calcd. for $C_{24}H_{27}NO_7$: C, 65.29; H, 6.16; N, 3.17. Found: C, 65.10; H, 6.03; N, 3.29.

Alkylation as above but in ethanol (3) at reflux for 15 hours gave a mixture including **10**. The nmr spectrum indicated some loss of C-3 $OCOCH_3$ (possibly due to transesterification) and dialkylation. Use of 1,5-diazabicyclo[5.4.0]undecene as the base, in DMF at 25° for 72 hours, gave a less pure and lower yield product.

N-Chloroacetyl-3,6-diacetylnormethylmorphine (**11**).

A mixture of **4** (0.36 g., 0.0010 mole) and potassium carbonate (0.180 g., 0.0013 mole) in dichloromethane, to which was added chloroacetyl chloride (0.11 g., 0.0010 mole), was left at 25° for 18 hours with stirring. Thin layer chromatography revealed one major and two minor components. The reaction mixture was washed with water, dilute hydrochloric acid, and saturated sodium chloride solution to leave mainly one component (tlc) after removal of solvent. Chromatography on silica gel and elution with chloroform gave the product (one component, tlc). Evaporation of the solvent and recrystallization from ether-petroleum ether (37-48°) gave solid, m.p. 123-130° which was recrystallized from ethyl acetate to give **11** (0.30 g., 0.00070 mole, 70%), m.p. 124-126°; nmr (deuteriochloroform): δ 4.1 (s, 2, CH_2Cl).

Anal. Calcd. for $C_{22}H_{22}ClNO_6$: C, 61.18; H, 5.15; N, 3.24. Found: C, 61.11; H, 5.16; N, 3.24.

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(11) Morphine has uv max (95% ethanol) 286 nm, changes to 300 nm with dilute aqueous sodium hydroxide.