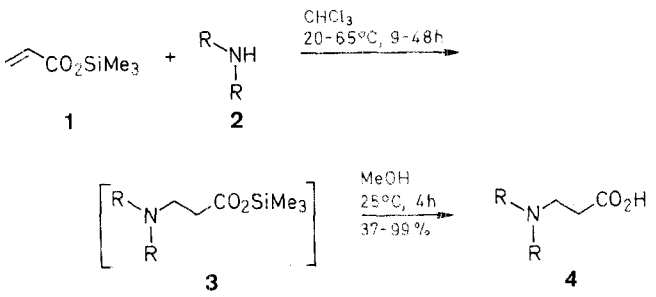
A Synthesis of *N*-Substituted β-Alanines: Michael Addition of Amines to Trimethylsilyl Acrylate

Stefan Kwiatkowski,*[1] Azhwarsamy Jeganathan, Thomas Tobin, David S. Watt

Department of Chemistry, Department of Veterinary Science,[2] and Maxwell H. Gluck Equine Research Center, University of Kentucky, Lexington, KY 40506, USA

The Michael addition of primary and secondary amines **2** to trimethylsilyl acrylate (**1**) afforded β-(alkylamino)- and β-(dialkylamino)-propionic acids **4**, respectively, in good yield.

In connection with the production of haptens of various pharmaceuticals and drugs of abuse, we required a convenient procedure for the modification of primary and secondary amines in order to attach a carboxylic acid functional group suitable for conjugation to bovine serum albumin. Although this type of modification[3,4] often involves the treatment of amines with succinic anhydride or methyl succinyl chloride these procedures are not always compatible with functionality elsewhere in the substrate, and in some cases afforded antibodies with reduced specificity in comparison with antibodies produced from β-alanine derivatives. We report that the reactions of trimethylsilyl acrylate (**1**) with various amines **2** provide convenient access to *N*-substituted β-alanines **4** via the intermediate trimethylsilyl esters **3** (Scheme A).

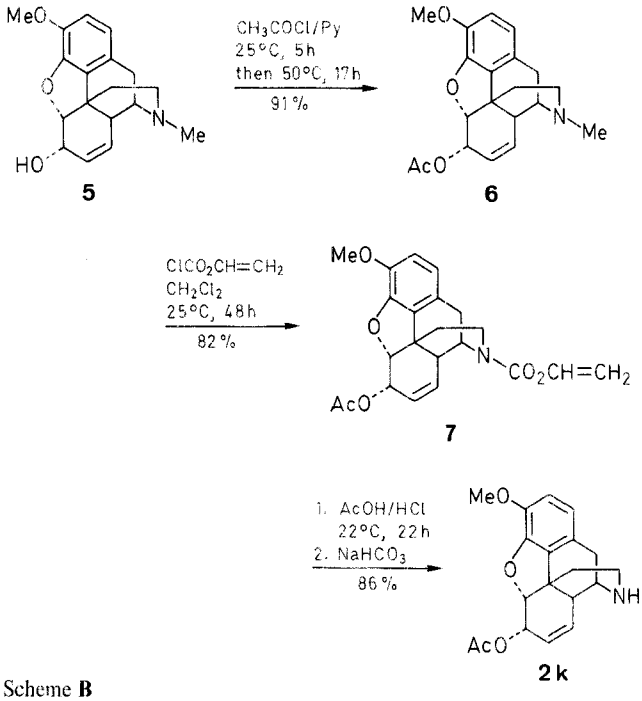


Scheme A

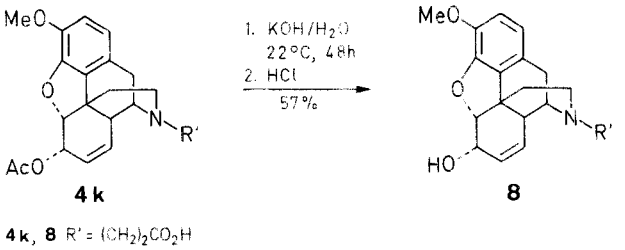
Although the Michael addition of amines **2** to acrylonitrile,[5] methyl acrylate, or ethyl acrylate[3,4] was known, the use of these methods for the synthesis of *N*-substituted β-alanines **4** required basic or acidic hydrolysis in order to liberate the free carboxylic acid. Procedures that avoided this hydrolysis step employed the addition of secondary *N*-(trimethylsilyl)amines to β-propiolactone[6,7] to give β-(dialkylamino)propionic acids, however this route required the synthesis of *N*-(trimethylsilyl)amines and the use of the carcinogenic β-propiolactone. Although the direct addition of amines to acrylic acid failed,[5] the addition of amines to trimethylsilyl acrylate (**1**)[8] provided the intermediate β-alanine trimethylsilyl esters **3** that were readily solvolyzed in methanol to give *N*-substituted β-alanines **4** in good yield (Tables 1, 2).

This new approach was particularly useful in the synthesis of new haptens for cocaine and acetylcodeine. Norcocaine (**2h**),[9] for example, was treated with 1.2 equivalents of trimethylsilyl acrylate (**1**) to afford the trimethylsilyl ester of norcocaine-8-propionic acid (**3h**), which was directly hydrolyzed to **4h**. As shown in Scheme B, conversion[10] of the 6-acetate derivative **6** of codeine (**5**) to the vinyl urethane **7**, and selective hydrolysis afforded the *N*-demethylated derivative **2k**. Subsequent treatment of **2k** with **1** and hydrolysis furnished the acid **4k** that was

saponified to afford **8**. As indicated in Table 1, the process accommodated a variety of primary and secondary amines having pK_b values in the range of 3 to 4 was successful in the synthesis of haptens of a variety of bioactive compounds.



Scheme B



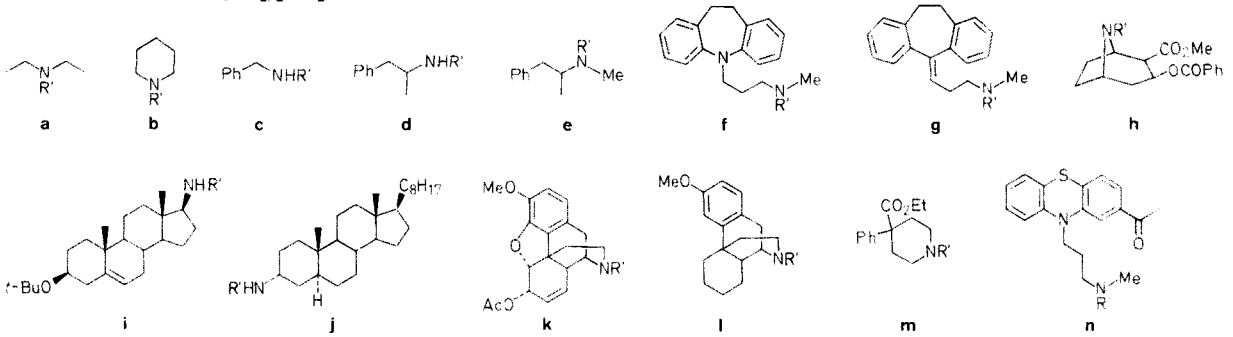
Addition of Amines 2 to Trimethylsilyl Acrylate (1) and Methanolysis of β-Alanine Trimethylsilyl Esters 3 to β-Alanines 4; General Procedure:
To a solution of amine **2** (0.3 mmol) in $CHCl_3$ (0.6 mL) (or $CDCl_3$ in cases where the reaction is monitored by ^{1}H-NMR) is added trimethylsilyl acrylate (**1**; 43 mg, 1.2 equiv or the amount indicated in Table 1), and the mixture is heated for the period of time and temperature specified in Table 1. The disappearance of starting amine is monitored by TLC (eluent, $CHCl_3$/MeOH, 4:1) or ^{1}H-NMR. When the reaction is complete, MeOH (1 mL) is added, and the resulting clear solution is stored at 22 °C for 4 h and concentrated to afford crude **4**. The product is purified by column chromatography on silica gel using $CHCl_3$/MeOH as the eluent (Tables 1, 2).

(5α,6α)-6-Acetoxy-7,8-didehydro-4,5-epoxy-3-methoxy-17-methylmorphinan (6):
To a solution of codeine monohydrate (**5**; 317 mg, 1 mmol) in anhydrous pyridine (5 mL) is added acetyl chloride (285 μL, 4 mmol), and the mixture is stirred under N_2 atmosphere for 5 h at 25 °C and 17 h at 50 °C. The pyridine is evaporated under reduced pressure and the semisolid residue is dissolved in water (3 mL). To this solution is added a solution of K_2CO_3 (1 g) in water (3 mL), and the oily product separated is extracted with Et_2O (3 × 15 mL). The ethereal extracts are dried ($MgSO_4$) and evaporated to afford **6** as a yellow solid; yield: 326 mg (91%); mp 132–133 °C (Lit.[11] 133.5 °C).

Table 1. Addition of Amines **2** to Trimethylsilyl Acrylate (**1**)

Amine[a] **2**	Reaction Conditions			Product[a]	Yield (%)	mp (°C)	Molecular Formula[b] or Lit. mp (°C)
	Ratio of 1:2	Time (h)	Temp. (°C)				
a	1.2	17	25	**4a**	99	[e]	136–138[12,c]
b	1.2	17	25	**4b**	99	[e]	82–83[12] (210–211)[12,c]
c	1.0	9	50	**4c**	37	[e]	182–183[12]
d	1.2	44	50	**4d**	53	181–182.5	$C_{12}H_{17}NO_2$ (207.3)
e	1.2	17	50	**4e**	83	oil	$C_{13}H_{19}NO_2$ (221.3)
f	1.2	17	50	**4f**	82	105–107 (dec.)	–[13,d]
g	1.2	17	50	**4g**	95	121–123 (dec.)	oil[13]
h	1.2	17	50	**4h**	88	oil	$C_{19}H_{23}NO_6$ (345.4)
i	1.1	40	65	**4i**	83	166–167	$C_{26}H_{43}NO_3$ (417.6)
j	1.1	40	65	**4j**	82	182–184	$C_{30}H_{53}NO_2$ (459.8)
k[14]	1.2	48	22	**4k**	92	178–181	$C_{22}H_{25}NO_6$ (399.5)
l	1.2	25	60	**4l**	59	oil	$C_{20}H_{27}NO_3$ (329.4)
m	2.0	24	20	**4m**	76	143–145	$C_{17}H_{23}NO_4$ (305.4)
n	2.0	48	20	**4n**	55	98–100	$C_{21}H_{24}N_2O_3S$ (384.5)

[a] **2a–k**, R' = H; **4a–k**, R' = $(CH_2)_2CO_2H$.



[b] All new compounds exhibited satisfactory high resolution mass spectra, deviation: ±0.001.
[c] Melting point of the hydrochloride salt.
[d] Not reported.
[e] Reaction conducted in NMR tube.

IR ($CDCl_3$): $\nu = 1730\,cm^{-1}$.

^1H-NMR ($CDCl_3$/TMS): $\delta = 2.16$ (s, 3H, $COCH_3$); 2.44 (s, 3H, NCH_3); 2.70–2.80 (m, 1H, H-14); 3.05 (d, 1H, $J = 19$ Hz, H-10β); 3.33–4.02 (m, 1H, H-9); 3.84 (s, 3H, OCH_3); 5.70 (d, 1H, $J = 7$ Hz, H-5); 5.15–5.23 (m, 1H, H-6); 5.44 (d, 1H, $J = 8$ Hz, H-8); 5.63 (d, 1H, $J = 8$ Hz, H-7); 6.53 (d, 1H, $J = 6.5$ Hz, H-2); 6.67 (d, 1H, $J = 6.5$ Hz, H-1).

^{13}C-NMR ($CDCl_3$/TMS): $\delta = 20.50$ (C-15), 21.09 ($\underline{C}H_3C{=}O$), 35.68 (C-10), 41.02 (C-14), 42.68 (C-13), 43.36 (NCH_3); 46.91 (C-16), 56.86 (OCH_3), 59.31 (C-9), 68.63 (C-6), 88.51 (C-5), 114.17 (C-8), 119.63 (C-7), 127.54 (C-11), 128.90 (C-1), 131.13 (C-12), 130.20 (C-2), 142.32 (C-3), 146.60 (C-4), 170.94 (C=O).

Vinyl (5α,6α)-6-Acetoxy-7,8-didehydro-4,5-epoxy-3-methoxy-17-morphinancarboxylate (7):

A solution of **6** (320 mg, 0.94 mmol) and vinyl chloroformate (501 mg, 400 μL, 4.70 mmol) in anhydrous CH_2Cl_2 (2 mL) is stirred under a nitrogen atmosphere for 48 h at 25°C. The dark brown mixture is evaporated to afford a semisolid residue, which is chromatographed on silica gel using EtOAc/hexane/$CHCl_3$ (1:1:1) to afford **7**; yield: 305 mg (82%); mp 178–181°C (decom.).

HRMS: *m/z*, $C_{22}H_{23}NO_6$, calc.: 397.1526; found: 397.1525 (M^+).

IR ($CDCl_3$): $\nu = 1725$, 1695 cm^{-1}.

^1H-NMR ($CDCl_3$/TMS): $\delta = 1.88–2.00$ (m, 2H, H-15); 2.16 (s, 3H, $COCH_3$); 3.87 (s, 3H, OCH_3); 4.04–4.18 (m, 1H, H-16); 4.50 (t, 1H, $J = 6$ Hz, H-9); 4.78–5.00 (m, 2H, $CH{=}\underline{C}H_2$); 5.08 (d, 1H, $J = 7$ Hz, H-5); 5.12–5.20 (m, 1H, H-6); 5.47 (d, 1H, $J = 8$ Hz, H-8); 5.70 (d, 1H, $J = 8$ Hz, H-7); 6.56 (d, 1H, $J = 6.5$ Hz, H-2); 6.70 (d, 1H, $J = 6.5$ Hz, H-1); 7.20–7.30 (m, 1H, $\underline{C}H = CH_2$).

^{13}C-NMR ($CDCl_3$/TMS): $\delta = 20.98$ ($\underline{C}OCH_3$), 29.59 (C-10), 35.20 (C-15), 38.39 (C-14), 39.48 (C-16), 43.20 (C-13), 50.94 (C-9), 56.85 (H_3CO), 67.92 (C-6), 88.04 (C-5), 96.14 ($CH{=}\underline{C}H_2$), 114.75 (C-2), 120.23 (C-1), 125.79 (C-11), 128.51 (C-8), 129.81 (C-12), 130.03 (C-7), 143.02 (C-3, $\underline{C}H{=}CH_2$), 146.50 (C-4), 153.0 ($\underline{C}O_2CH{=}CH_2$), 171.14 ($\underline{C}OCH_3$).

(5α,6α)-6-Acetoxy-7,8-didehydro-4,5-epoxy-3-methoxymorphinan (17-Norcodeine Acetate, 2k):

A solution of **7** (130 mg, 0.3 mmol) in glacial HOAc containing two drops of conc. HCl is stirred at 22°C for 22 h. The solvents are evaporated under reduced pressure (bath temp. below 50°C), and water (3 mL) is added to the white, crystalline residue. The mixture is filtered to remove insoluble material and the clear filtrate is treated with an excess of solid $NaHCO_3$, causing separation of oily product, which is extracted with Et_2O (3 × 15 mL). The combined ethereal extracts are dried ($MgSO_4$), evaporated, and the crude product is purified by chromatography on silica gel using $CHCl_3$/MeOH (4:1) to give **2k** as a colorless oil; yield: 44 mg (86%).

HRMS: *m/z*, $C_{19}H_{21}NO_4$ calc.: 327.1471; found: 327.1472 (M^+).

IR (film): $\nu = 3310$, 1725 cm^{-1}.

^1H-NMR ($CDCl_3$/TMS): $\delta = 1.84–1.96$ (m, 2H, H-15), 2.15 (s, 3H, $COCH_3$); 2.18–2.36 (m, 2H, NH + H-10α); 2.60–2.74 (m, 1H, H-10β); 2.80–3.02 (m, 3H, H-14, 16); 3.61–3.72 (m, 1H, H-9); 3.87 (s, 3H,

Table 2. Spectral Data of β-Alanine Derivatives **4d–n**

Product	IR ($CDCl_3$) ν (cm^{-1})	^1H-NMR ($CDCl_3$/TMS) δ, J (Hz)	^{13}C-NMR ($CDCl_3$/TMS) δ
4d	1580	1.27 (d, 3H, $J = 6.4$); 2.57 (t, 2H, $J = 5.5$); 2.78 (dd, 1H, $J = 15.8$, 7.8); 3.00–3.39 (m, 4H); 7.16–7.33 (m, 4H); 7.00–8.00 (br s, 2H)	16.38, 32.32, 40.24, 42.37, 55.30, 127.52, 129.31, 129.88, 137.15, 177.56
4e	1710, 1600	1.10 (d, 3H, $J = 6.4$); 2.56 (s, 3H); 2.44–2.62 (m, 3H); 3.05–3.45 (m, 4H); 7.15–7.35 (m, 5H); 12.58 (br s, 1H)	13.16, 31.59, 35.36, 38.34, 50.07, 61.34, 127.21, 129.16, 129.72, 138.16, 175.70
4f	1710, 1590	1.78–1.95 (m, 2H); 2.31 (s, 3H); 2.30–2.40 (m, 2H); 2.70–2.82 (m, 4H); 3.12 (s, 4H); 3.73 (t, 2H, $J = 5.5$); 6.85–7.12 (m, 8H); 11.72 (br s, 1H)	23.31, 31.08, 32.36, 40.04, 48.14, 53.03, 54.37, 120.23, 123.42, 127.09, 130.54, 134.70, 148.25, 175.25
4g	1705, 1600	2.37 (s, 3H); 2.35–2.50 (m, 4H); 2.70–2.98 (m, 6H); 3.17–3.40 (m, 2H); 5.76 (t, 1H, $J = 7$); 6.97–7.24 (m, 8H); 9.70 (br s, 1H)	24.70, 30.38, 31.77, 33.54, 39.33, 52.54, 55.25, 125.75, 126.17, 126.26, 127.56, 127.85, 128.03, 128.42, 128.67, 130.26, 137.18, 139.44, 139.52, 140.57, 146.13, 174.80
4h	1735, 1720, 1625	1.86–2.30 (m, 5H); 2.40–2.60 (m, 3H); 2.67 (t, 2H, $J = 6.4$); 3.16–3.24 (m, 1H); 3.60 (br s, 1H); 3.74 (s, 4H); 5.30–5.42 (m, 1H); 7.40–7.60 (m, 3H); 7.95–8.05 (m, 2H); 12.70 (br s, 1H)	25.19, 26.10, 31.58, 35.40, 48.63, 50.17, 52.41, 59.04, 63.27, 66.24, 128.96, 128.99, 130.16, 133.83, 166.52, 171.05, 173.87
4i	1585	0.83 (s, 3H); 0.99 (s, 3H); 1.18 (s, 9H); 2.40–2.53 (m, 2H); 2.82–3.02 (m, 3H); 3.18–3.35 (m, 2H); 5.27–5.32 (m, 1H); 11.57 (br s, 1H)	18.62, 19.47, 21.04, 25.96, 26.48, 28.7, 31.25, 31.64, 32.06, 32.3, 32.47, 36.9, 38.17, 42.32, 44.11, 44.51, 49.52, 50.2, 60.6, 71.76, 73.84, 121.34, 142.27, 177.82
4j	1580	0.62 (s, 3H); 0.78 (s, 3H); 0.84 (d, 6H, $J = 7.5$); 0.87 (d, 3H, $J = 7.5$); 2.50–2.60 (m, 2H); 3.00–3.10 (m, 2H); 3.20–3.30 (m, 1H); 11.12 (br s, 1H)	11.50, 12.25, 18.86, 21.09, 22.86, 23.14, 23.53, 24.19, 28.30, 28.57, 30.12, 31.94, 32.0, 32.34, 35.67, 36.13, 36.5, 39.6, 39.8, 40.2, 42.9, 43.0, 53.8, 54.0, 56.8, 177.8
4k	1725, 1705, 1595	1.90–2.02 (m, 1H); 2.15 (s, 3H); 2.18–2.35 (m, 1H); 2.56–2.75 (m, 4H); 2.96–3.24 (m, 5H); 3.85 (s, 3H); 3.85–3.96 (m, 1H); 5.10 (d, 1H, $J = 6.7$); 5.14–5.22 (m, 1H); 5.43 (d, 1H, $J = 8$); 5.68 (d, 1H, $J = 8$); 6.60 (d, 1H, $J = 6.5$); 6.72 (d, 1H, $J = 6.5$); 10.30 (br s, 1H)	20.98, 22.48, 31.28, 33.74, 38.50, 42.28, 44.82, 51.16, 56.95, 58.10, 67.98, 87.77, 114.98, 120.17, 128.05, 129.90, 130.16, 133.74, 143.27, 147.28, 171.11, 175.97
4l	1710, 1600	1.03–1.59 (m, 7H); 1.64 (d, 1H, $J = 11.6$); 1.97 (dt, 1H, $J = 18.8$, 5.8); 2.13 (dt, 1H, $J = 11.6$, 3); 2.36 (d, 1H, $J = 13$); 2.44 (t, 2H, $J = 7.2$); 3.02 (s, 2H); 3.11 (d, 1H, $J = 11.6$); 3.24 (t, 2H, $J = 7.2$); 3.47 (s, 1H); 3.78 (s, 3H); 6.76 (dd, 1H, $J = 8$, 2.4); 6.81 (d, 1H, $J = 2.4$); 7.07 (d, 1H, $J = 8$); 9.34 (br s, 1H)	21.72, 24.52, 25.80, 25.99, 30.50, 34.54, 36.73, 39.40, 42.13, 44.82, 50.65, 55.12, 56.99, 111.0, 111.60, 126.19, 128.75, 139.48, 158.72, 175.08
4m	1705, 1605	1.17 (t, 3H, $J = 7.1$); 2.10–2.30 (m, 2H); 2.50–2.70 (m, 6H); 2.95 (t, 2H, $J = 6$); 3.15–3.30 (m, 2H); 4.14 (q, 2H, $J = 7.1$); 7.20–7.40 (m, 5H); 9.90 (br s, 1H)	14.16, 31.86, 48.50, 50.46, 54.12, 61.66, 126.18, 127.96, 129.26, 141.66, 174.11, 176.21
4n	1675	1.96–2.12 (m, 2H); 2.34 (s, 3H); 2.40 (t, 2H, $J = 6.8$); 2.56 (s, 3H); 2.76 (t, 4H, $J = 6.8$); 3.96 (t, 2H, $J = 6.8$); 6.87–7.50 (m, 7H)	22.75, 26.43, 30.68, 40.30, 44.60, 52.89, 53.44, 114.17, 116.11, 123.33, 123.53, 124.40, 127.34, 127.74, 127.99, 132.80, 136.43, 144.25, 145.34, 174.96, 197.77

OCH_3); 5.05 (d, 1 H, J = 7 Hz, H-5); 5.14–5.23 (m, 1 H, H-6); 5.42 (d, 1 H, J = 8.2 Hz, H-8); 5.65 (d, 1 H, J = 8.2 Hz, H-7); 6.57 (d, 1 H, J = 6.8 Hz, H-2); 6.68 (d, 1 H, J = 6.8 Hz, H-1).

^{13}C-NMR ($CDCl_3$/TMS): δ = 21.10 ($CO\underline{C}H_3$), 31.50 (C-10), 36.30 (C-15), 38.78 (C-14), 41.47 (C-16), 43.95 (C-13), 52.45 (C-9), 56.88 (OCH_3), 68.49 (C-6), 89.02 (C-5), 114.20 (C-2), 119.68 (C-1), 127.63 (C-11), 129.04 (C-8), 130.00 (C-7), 131.02 (C-12), 142.52 (C-3), 147.20 (C-4), 171.27 (C=O).

(5α,6α)-7,8-Didehydro-6-hydroxy-4,5-epoxy-3-methoxy-17-morphinanpropionic Acid (8):

A solution of **4k** (71.2 mg, 0.18 mmol) and KOH (19.3 mg, 0.344 mmol) in water (1 mL) is stirred at 22 °C for 48 h and then treated with 1 N HCl (345 μL). The mixture is evaporated to dryness under reduced pressure (bath temperature below 50 °C) and finally dried under high vacuum to afford white crystals from which the product is extracted with $CHCl_3$ (3 × 5 mL). The residue obtained after evaporation of the solvent is chromatographed on silica gel using $CHCl_3$/MeOH (3:1) as eluent; yield: 36.8 mg (57%); mp 110 °C (decom.).

HRMS: m/z, $C_{20}H_{23}NO_5$ calc.: 357.1576; found: 357.1578.

IR ($CDCl_3$): ν = 3500, 3100–2300, 1710 cm^{-1}.

^{1}H-NMR ($CDCl_3$/TMS): δ = 1.95–2.07 (m, 1 H, H-15β); 2.13–2.32 (m, 1 H, H-15α); 2.56–2.77 (m, 4 H, H-10α, 14 + CH_2CO_2); 2.88–3.16 (m, 5 H, H-10α, 16 + $NC\underline{H}_2CH_2$); 3.75–3.83 (m, 1 H, H-9); 3.84 (s, 3 H, OCH_3); 4.18–4.26 (m, 1 H, H-6); 4.95 (d, 1 H, J = 6 Hz, H-5); 5.28 (d, 1 H, J = 8 Hz, H-8); 5.78 (d, 1 H, J = 8 Hz, H-7); 6.62 (d, 1 H, J = 6.8 Hz, H-2); 6.70 (d, 1 H, J = 6.8 Hz, H-1).

^{13}C-NMR ($CDCl_3$/TMS): δ = 22.69 ($\underline{C}H_2CO_2$), 30.07 (C-10), 34.53 (C-15), 39.72 (C-14), 42.95 (C-16), 44.08 (C-13), 51.05 ($NC\underline{H}_2CH_2$), 56.60 (OCH_3), 58.14 (C-9), 66.38 (C-6), 90.98 (C-5), 114.01 (C-2), 120.47 (C-1), 126.55 (C-8), 127.98 (C-11), 131.02 (C-12), 135.24 (C-7), 143.38 (C-3), 147.30 (C-4), 174.49 (C=O).

We thank the Kentucky Equine Drug Research Council and the Kentucky State Racing and Harness Racing Commissions for their generous support.

Received: 19 April 1989; revised: 19 June 1989

(1) On leave from Warsaw Technical University, Warsaw, Poland. Author to whom correspondence should be directed.
(2) Published as Kentucky Agricultural Experiment Station article with approval of the Dean and Director, College of Agriculture and Kentucky Agricultural Experiment Station. This is publication #157 from the Kentucky Equine Drug Testing and Research Programs, Department of Veterinary Science and the Graduate Center for Toxicology.
(3) Hubbard, J.W., Midha, K.K., McGilveray, I.J., Cooper, J.K. *J. Pharm. Sci.* **1978**, *67*, 1563.
(4) Hubbard, J.W., Midha, K.K., Cooper, J.K., Charette, C. *J. Pharm. Sci.* **1978**, *67*, 1571.
(5) Suminov, S.I., Kost, A.N. *Russ. Chem. Rev.* **1969**, *38*, 892.
(6) Itoch, K., Sahai, S., Ishii, Y. *J. Org. Chem.* **1965**, *31*, 3948.
(7) Papiri, A., Ricci, A., Taddei, M., Secoui, G., Denbech, P. *J. Chem. Soc. Perkin Trans. 1* **1984**, 2261.
(8) Mironov, V.F., Fedotov, N.S. *Khim. Geterosikl. Soedin, Akad. Nauk. Latv. SSR* **1966**, 453; *C.A.* **1967**, *66*, 76077.
(9) Baldwin, S.W., Jeffs, P.W., Natarajan, S. *Synth. Commun.* **1977**, *7*, 79.
(10) Olofson, R.A., Schnur, R.C., Bunes, L., Pepe, J.P. *Tetrahedron Lett.* **1977**, 1567.
(11) *Dictionary of Organic Compounds*, 5th ed., Vol. 2, Buckingham, J. (ed.), Chapman & Hall, London, 1982, p. 1266.
(12) Gresham, T.L., Jansen, J.E., Shaver, F.W., Bankert, R.A., Fiedorek, F.T. *J. Am. Chem. Soc.* **1951**, *73*, 3168.
(13) Hubbard, J.W., Midha, K.K., Cooper, J.K., Charette, C. *J. Pharm. Sci.* **1978**, *67*, 1571.
(14) Olofson, R.A., Martz, J.T., Senet, J.P., Piteau, M., Malfroot, T. *J. Org. Chem.* **1984**, *49*, 2061.