Pyrrolizin-3-one

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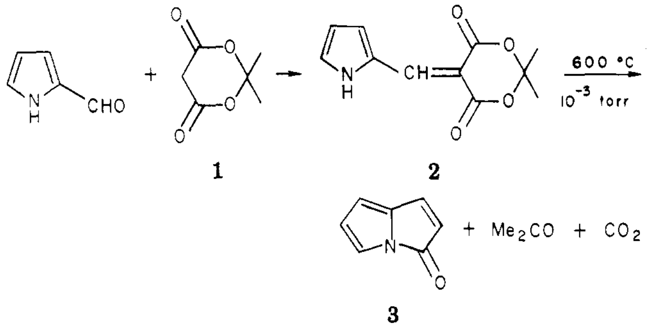
Some years ago, Flitsch and Neumann prepared pyrrolizin-3-one (**3**), in 14% overall yield, by condensation of malonic acid with pyrrole-2-carboxaldehyde and subsequent cyclization in acetic anhydride.[1] However, due to its sensitivity and its relatively high volatility, it proved difficult to isolate and purify the product, and so it has found little subsequent application in synthesis. This note describes a simple and efficient preparation of **3** which depends on the generation of the lactam function by gas-phase pyrolysis of a derivative of 2,2-dimethyl-1,3-dioxane-4,6-dione[2] (Meldrum's acid, **1**). Such reactions have been observed in solution by Danishevsky[3] and by Lesher;[4] gas-phase pyrolysis of Meldrum's acid derivatives has been extensively studied by Brown and co-workers.[5] For the present example, these short-contact-time gas-phase conditions were chosen because they are particularly suitable for the preparation of sensitive compounds. In addition, the workup problem of separating the product from an excess of inert, involatile solvent is avoided in this way.

Reaction of pyrrole-2-carboxaldehyde with Meldrum's acid at room temperature overnight gives the condensation product **2**[6] as yellow crystals (84%). Flash vacuum pyrolysis of **2** at 500 °C generates an acetone solution of pyrrolizin-3-one (**3**) together with some unreacted starting material. The conversion is complete at 600 °C, however, and the pure heterocycle is obtained directly by distillation of the pyrolysate (88%).



1 **2** **3**

Pyrrolizin-3-one (**3**) is a deep red mobile liquid. It is stable indefinitely at −30 °C but rapidly becomes dark on exposure to the air at room temperature.

Experimental Section

2,2-Dimethyl-5-(pyrrol-2-ylidine)-1,3-dioxane-4,6-dione (2).[6] A solution of pyrrole-2-carboxaldehyde (4.3 g, 50 mmol) and 2,2-dimethyl-1,3-dioxane-4,6-dione (**1**; 7.2 g, 50 mmol) in benzene (130 mL) was treated with acetic acid (1 mL) and piperidine (1 mL) and set aside overnight. The yellow crystals which had formed were filtered, washed thoroughly with the filtrate, and dried in vacuo over phosphoric anhydride to give **2** (9.29 g, 84%) in sufficient purity for the next stage of the sequence: mp 178–180 °C (from ethanol)(lit.[6] mp 182 °C); ^{1}H NMR (CDCl$_3$) δ 8.25 (s, 1 H), 7.43 (m, 1 H), 7.10 (m, 1 H), 6.52 (m, 1 H), 1.75 (s, 6 H); ^{13}C NMR (CDCl$_3$) δ 164.04 (q), 143.12, 131.89, 130.09, 114.23, 104.03 (q), 100.12 (q), 35.85 (q) 27.00.

Pyrrolizin-3-one (3).[1] Freshly prepared **2** (4.42 g, 20 mmol) was sublimed at 120–140 °C (10^{-3} torr) over a period of 4 h into a horizontal 30 × 2.5 cm silica tube held at 600 °C. The products were condensed in a liquid nitrogen trap at the exit point of the furnace. At the end of the pyrolysis, the trap was rinsed out with some acetone which was subsequently evaporated at the water pump. Bulb-to-bulb distillation of the residue at 130 °C (16 torr) [lit.[1] bp 35–40 °C (0.05 torr)] gave pure pyrrolizin-3-one (**3**): 2.10 g (88%); ^{1}H NMR (CDCl$_3$) δ 7.04 (d, 1 H, J = 6 Hz), 6.85 (t, 1 H, J = 2 Hz), 5.95 (d, 2 H, J = 2 Hz), 5.63 (d, 1 H, J = 6 Hz); ^{13}C NMR (CDCl$_3$) δ 165.45 (q), 138.06, 136.75 (q), 121.82, 118.68, 115.25, 111.42; mass spectrum, m/e 119 (M$^+$, 100%), 91 (59), 64 (41), 63 (22). Anal. Calcd for C_7H_5NO: C, 70.59; H, 4.20; N, 11.76. Found: C, 70.68; H, 4.28; N, 11.74.

Registry No. 1, 2033-24-1; **2**, 23111-03-7; **3**, 34610-37-2; pyrrole-2-carboxaldehyde, 1003-29-8.

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Hydroxyalkylation and Acylation Reactions of Methyl Hippurate

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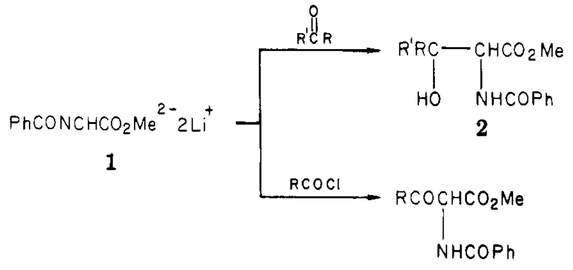
Our interest in the use of α-amino-β-hydroxy and α-amino-β-keto esters as synthetic intermediates for heterocyclic amino acids related to furanomycin and steptolutine led us to examine the reactions of the lithio dianion of methyl hippurate (**1**) with carbonyl compounds (**1** → **2**, hydroxyalkylation) and with acid chlorides (**1** → **3**, acylation).[1] We have found that hydroxyalkylation proceeds readily in high yield[2] and that, contrary to an earlier report,[3] the acylation reaction (**1** → **3**) can be effected in good yield with most acyl halides.



1 **2** **3**

Lithio dianion **1** is readily prepared by treatment of methyl hippurate at −78 °C with lithium diisopropylamide (LDA) in THF containing TMEDA as reported by Krapcho.[4] In our studies, we also investigated the use of hindered amide bases other than LDA, including lithium tetramethylpiperidide (LTMP) and lithium hexamethyl-

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[1] Some of the results reported here were presented at the 179th National Meeting of the American Chemical Society, Houston, TX, Mar 24–28, 1980, Abstract ORGN 17, and the 35th Southwest Regional Meeting of the American Chemical Society, Austin, TX, Dec 5–7, 1979, Paper 193.

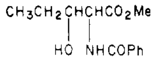
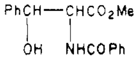
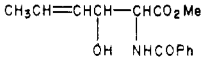
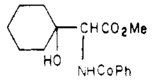
[2] Following our initial studies in this area, the hydroxyalkylation of the dianion of *N*-(carbobenzoxy)glycine ethyl ester was reported. Shanzer, A.; Somekh, L.; Butina, D. *J. Org. Chem.* **1979**, *44*, 3967.

[3] Evans, D. A.; Sidebottom, P. J. *J. Chem. Soc., Chem. Commun.* **1978**, 753.

[4] Krapcho, A. P.; Dundulis, E. A. *Tetrahedron Lett.* **1976**, 2205. We found no evidence that dianion formation was limiting the yields of our reactions as was reported to be the case by Evans and Sidebottom[3] in their studies with the dianion of ethyl hippurate.

0022-3263/81/1946-2809$01.25/0

Table I. Hydroxyalkylation of Lithio Dianion 1

compd	base[a]	[anion], mM	temp, °C	product[b]	isolated yield, %
propionaldehyde	LDA	33	−78	 $\mathrm{CH_3CH_2\underset{HO}{C}H\underset{NHCOPh}{C}HCO_2Me}$ **2a**	78
	LHMDS	33	−78		72
benzaldehyde	LDA	33	−78	 $\mathrm{Ph\underset{OH}{C}H{-}\underset{NHCOPh}{C}HCO_2Me}$ **2b**	72
crotonaldehyde	LDA	33	−78	 $\mathrm{CH_3CH{=}CH\underset{OH}{C}H{-}\underset{NHCOPh}{C}HCO_2Me}$ **2c**	91
	LHMDS	33	−78		86
cyclohexanone	LDA	6.7	−78 to 0[c]		77
	LDA	33	−78 to +25[d]		38

[a] LDA = lithium diisopropylamide, LHMDS = lithium hexamethyldisilazide. [b] The products from reaction with aldehydes were an ~1:1 diastereomeric mixture as determined by ^{13}C NMR spectra. [c] Reaction was maintained at −78 °C for 15 min and then warmed to 0 °C before being quenched. [d] Reaction at this anion concentration gave some decomposition upon warming.

Table II. Acylation Reactions of Lithio Dianion 1

acid chloride	base[a,b]	[anion], mM	mmoles of anion	product	isolated yield, %
CH_3COCl	LHMDS	33	0.5	$CH_3COCH(NHCOPh)CO_2Me$ (**3a**)	28
CH_3CH_2COCl	LHMDS	33	0.5	$CH_3CH_2COCH(NHCOPh)CO_2Me$ (**3b**)	48
	LDA	33	0.5		30
	LTMP	33	0.5		33
BuCOCl	LHMDS	33	0.5	$BuCOCH(NHCOPh)CO_2Me$ (**3c**)	58
	LHMDS	6.7	0.5		59
$CH_2{=}CH(CH_2)_2COCl$	LHMDS	6.7	1.0	$CH_2{=}CH(CH_2)_2COCH(NHCOPh)CO_2Me$ (**3d**)	69
	LHMDS	10.3[c]	5.1		61
PhCOCl	LHMDS	6.7[d]	0.5	$PhCOCH(NHCOPh)CO_2Me$ (**3e**)	45

[a] LHMDS = lithium hexamethyldisilazide, LDA = lithium diisopropylamide, and LTMP = lithium tetramethylpiperidide. [b] All reactions were conducted at −78 °C. [c] Reaction on this scale at a 33 mM anion concentration gave a lower yield. [d] Only a 15% yield was obtained at 33 mM anion concentration.

disilazide (LHMDS). Although the hydroxyalkylation reaction (1 → 2) appears to be relatively insensitive to the base used, the acylation reaction (1 → 3) is much cleaner and gives higher yields of product if lithium hexamethyldisilazide is used as the base for deprotonation.

Dianion 1 reacted rapidly with aldehydes at −78 °C to give the β-hydroxy derivatives 2 in quite high yield (Table I). Under these conditions the reaction with cyclohexanone was distinctly slower; however, this reaction can be effected by slowly warming the solution prior to quenching. The reaction of dianion 1 with aldehydes gives a mixture of both possible diastereomers in a ratio close to 1:1 (as determined by ^{13}C NMR spectroscopy). Reaction of the dianion 1 with crotonaldehyde gave only the 1,2-addition product with no evidence for any conjugate addition.

Our studies on the acylation reaction (1 → 3) show that, under appropriate conditions, the lithio dianion 1 can be acylated in good yields by using acid chlorides (Table II). We have found that reaction at concentrations higher than those shown in Table II reduces the yields and reproducibility of these acylations. The results also show that acetyl chloride gives significantly lower yields than the higher homologues.[5]

Experimental Section

General Procedures. Infrared spectra were determined on a Perkin-Elmer Model 297 infrared spectrophotometer. High-resolution mass spectra were determined on a CEC Model 23-110B spectrometer under the supervision of Dr. R. Grigsby.

^{1}H nuclear magnetic resonance spectra were determined on a Varian Associates Model T-60, FT-80, or XL-200 spectrometer. The solvent used is stated for each spectrum, and tetramethylsilane was used as an internal reference. Chemical shifts are reported as δ values in parts per million relative to Me_4Si (δ 0.00). ^{13}C nuclear magnetic resonance spectra were determined on a JEOL PFT-100 spectrometer in the FT mode operating at 25.034 MHz with a Nicolet 1085 data system. Deuteriochloroform was used as the solvent, and Me_4Si was used as the internal standard. Chemical shifts are reported as δ values in parts per million relative to Me_4Si. Multiplicities were obtained from single-frequency, off-resonance decoupled spectra.

All reactions involving organometallic reagents were conducted under an argon atmosphere by using an Ace-Burlitch inert atmosphere system.

General Procedure for the Preparation of the Lithio Dianion of Methyl Hippurate (1). A solution of 1.1 mmol of the selected hindered amine (diisopropylamine, isopropylcyclohexylamine, 2,2,6,6-tetramethylpiperidine, or 1,1,1,3,3,3-hexamethyldisilazane) and 1.1 mmol (128 mg) of TMEDA in 10 mL of THF was cooled to −78 °C. Then *n*-butyllithium (0.748 mL of 1.47 M *n*-butyllithium, 1.1 mmol) was added dropwise over approximately a 3-min period, and the solution was stirred for 30 min to allow for formation of the amide base. Methyl hippurate (97 mg, 0.5 mmol) in 4 mL of THF was added dropwise over approximately a 4-min period. The solution immediately became light yellow and, after approximately half of the methyl hippurate solution had been added, a solid yellow precipitate began forming. The solution was stirred for 1 h to allow formation of the lithio dianion of methyl hippurate (MHDA). Solutions of MHDA at

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(5) Evans and Sidebottom[3] suggested that acid chlorides are not suitable acylating agents for the lithio dianion of ethyl hippurate[6] on the basis of their obtaining only a 15% yield with acetyl chloride. Our reaction conditions increase the yield of this reaction (Table II), but acetyl chloride still gives the lowest yield observed in our studies.

(6) We have found the behavior of the lithio dianion of methyl hippurate (1) and the lithio dianion of ethyl hippurate to be similar. We utilized the methyl derivative because of the greater spectral simplicity of the products.

6.7 mM concentration were prepared in the same manner by using more THF as solvent.

General Procedure for Hydroxyalkylation Reactions of MHDA. To a vigorously stirred THF solution of MHDA (from 0.5 mmol of methyl hippurate) at −78 °C was added, dropwise, 1 mL of a 0.55 M THF solution of the appropriate aldehyde. The solution was stirred at −78 °C for 2 h, at which point the solution was translucent but cloudy white. The reaction was quenched at −78 °C by the addition of 10 mL of 2 N hydrochloric acid, at which point the solution became completely clear and water white. The THF layer was separated from the acidic aqueous layer, which was then extracted with ether. The combined organic layers were washed with water until the aqueous washings were neutral to pH paper and then with brine. The organic layer was dried over magnesium sulfate, filtered, and concentrated at reduced pressure. The product was isolated by preparative layer chromatography using plates coated with silica gel PF-254 (E. Merck).

Methyl 2-(Benzoylamido)-3-hydroxypentanoate (2a). Propionaldehyde was added to MHDA prepared from LDA to give, after repeated preparative layer chromatography (PLC, silica gel, ether, and then PLC, silica gel, ether–hexane, 9:1), 99 mg (78%) of **2a**. The ^{1}H NMR spectral data are reported for one diastereomer of undetermined stereochemistry. This diastereomer was obtained by fractionation with ether: ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.05 (t, 3 H, J = 7.3 Hz, $CH_2C\mathbf{H}_3$), 1.56 (q, 2 H, J = 7.3 Hz, $C\mathbf{H}_2CH_3$), 3.84 (s, 3 H, OCH_3), 3.99 (dt, 1 H, J = 6.8 Hz, J = 3.1 Hz, $\mathbf{H}COH$), 4.91 (dd, 1 H, J = 7.1 Hz, J = 3.1 Hz, $NC\mathbf{H}CO_2$), 7.15 (br s, 1 H, NH), 7.29 (s, 1 H, OH), 7.43–7.54 (m, 3 H, aryl H's), 7.83–7.87 (m, 2 H, ortho aryl H's); ^{13}C NMR ($CDCl_3$) δ 10.3 and 10.4 (C-5), 26.6 and 27.1 (C-4), 52.6 (OCH_3), 56.3 and 57.7 (C-2), 73.6 and 74.6 (C-3), 127.3, 128.6, 131.8, and 132.0, 133.4 and 133.7, 167.9 (CONH), 171.0 (COO); IR (KBr) 3300 (NH, OH), 1744 ($C{=}O$), 1641 cm^{-1} ($C{=}O$); mass spectrum, calcd for $C_9H_7O_2N$ ($M^+ - RCHO - MeOH$) *m/e* 161.0477, found *m/e* 161.0475, *m/e* (relative intensity) 222 (2), 194 (5), 193 (38), 192 (4), 162 (4), 161 (40), 133 (8), 122 (4), 106 (10), 105 (100), 78 (2), 77 (36), 76 (2), 51 (8).

Methyl 2-(Benzoylamido)-3-hydroxy-3-phenylpropionate (2b). Benzaldehyde was added to MHDA prepared from LDA to give, after chromatography (PLC, silica gel, ether, and then PLC, silica gel, ether–CH_2Cl_2, 1:1), 109 mg (72%) of **2b** as a mixture of two diastereomers. The following spectral data are reported for one diastereomer of undetermined stereochemistry. This diastereomer was obtained by fractionation with methylene chloride: ^{1}H NMR ($CDCl_3$, 200 MHz) δ 3.76 (s, 3 H, OCH_3), 4.69 (s, 1 H, OH), 5.24 (dd, 1 H, J = 7.2 Hz, J = 3.4 Hz, $NCHCO_2$), 5.39 (d, 1 H, J = 3.4 Hz, $C_6H_5C\mathbf{H}OH$), 6.97 (d, 1 H, J = 7 Hz, NH), 7.28–7.62 (m, 3 H, aryl H's), 7.71–7.78 (m, 2 H, ortho aryl H's); ^{13}C NMR ($CDCl_3$) δ 52.6 (OCH_3), 59.6 (C-3), 75.3 (C-2), 126.0, 127.2, 128.1, 128.3, 128.6, 132.1, 133.2, 139.2, 168.5 (CONH), 170.1 (COO); IR (KBr) 3350 (NH, OH), 1748 ($C{=}O$), 1644 cm^{-1} ($C{=}O$); mass spectrum, calcd for $C_{10}H_{11}O_2N$ ($M^+ - PhCHO$) *m/e* 193.0739, found *m/e* 193.0732, *m/e* (relative intensity) 194 (6), 193 (49), 162 (2), 161 (40), 149 (4), 134 (4), 132 (15), 107 (8), 106 (15), 105 (100), 79 (11), 78 (4), 77 (49), 76 (4), 51 (11), 50 (4).

(*E*)-Methyl-2-(benzoylamido)-3-hydroxy-4-hexenoate (2c). Crotonaldehyde was added to MHDA prepared from LDA to give, after repeated chromatography (PLC, silica gel, ether, and then PLC, silica gel, ether–hexane, 9:1), 120 mg (91%) of **2c** as a mixture of diastereomers: ^{1}H NMR ($CDCl_3$, 80 MHz) δ 1.69 (dd, 3 H, J = 5.9 Hz, J = 1 Hz, ${=}CCH_3$), 3.80 (s, 3 H, OCH_3), 4.50–5.02 (m, 2 H, $HOC\mathbf{H}(N)C\mathbf{H}CO_2$), 5.59–5.73 (m, 2 H, $HC{=}CH$), 6.95–7.15 (br s, 1 H, NH), 7.26 (s, 1 H, OH), 7.41–7.56 (m, 3 H, aryl H's), 7.76–7.88 (m, 2 H, ortho aryl H's); ^{13}C NMR ($CDCl_3$) δ 17.8 (C-6), 52.7 (OCH_3), 57.1 and 58.3 (C-2), 72.7 and 73.9 (C-3), 127.2, 128.2, 128.6, 129.5, 132.0, 133.3, 168.2 (CONH), 171.2 (COO); IR (film) 3400 (NH, OH), 1755 ($C{=}O$), 1650 cm^{-1} ($C{=}O$); mass spectrum, calcd for $C_{12}H_{14}O_2N$ ($M^+ - CO_2Me$) *m/e* 204.1025, found *m/e*, 204.1028, *m/e* (relative intensity) 204 (1), 194 (2), 193 (23), 162 (2), 161 (15), 135 (2), 134 (11), 133 (4), 106 (7), 105 (100), 78 (3), 77 (36), 51 (10), 50 (4).

Methyl 2-(Benzoylamido)-2-(1-hydroxycyclohexyl)acetate (2d). To a 0.1 M solution of MHDA (0.5 mmol) prepared from LDA at −78 °C was added 1 mL of a 0.55 M THF solution of cyclohexanone. The solution was warmed to −25 °C for 2 h and then quenched at −25 °C with 10 mL of 2 N hydrochloric acid. Isolation by chromatography (PLC, silica gel, ether) gave 56 mg (38%) of **2d**: mp 113–114 °C; ^{1}H NMR ($CDCl_3$, 80 MHz) δ 1.58 (br s, 10 H, cyclohexyl H's), 1.52 (s, 1 H, OH), 3.79 (s, 3 H, OCH_3), 4.80 (d, 1 H, J = 8.8 Hz, $OC\mathbf{H}C(N)CO_2$), 7.26 (s, 1 H, NH), 7.42–7.57 (m, 5 H, aryl H's), 7.77–7.89 (m, 2 H, ortho aryl H); ^{13}C NMR ($CDCl_3$) δ 21.7 (C-3′), 25.4 (C-4′), 34.5 and 35.4 (C-2′), 52.2 (OCH_3), 59.2 (C-2), 73.0 (C-1′), 127.3, 128.5, 131.8, 133.7, 167.5 (CONH), 172.3 (COO); mass spectrum, *m/e* calcd for $C_{14}H_{18}O_2N$ ($M^+ - CO_2Me$) *m/e* 232.1338, found *m/e* 232.1350, *m/e* (relative intensity) 232 (4), 196 (6), 195 (45), 162 (6), 161 (50), 133 (14), 106 (9), 105 (100), 99 (3), 81 (5), 72 (28).

When the reaction was run with 0.5 mmol of MHDA (6.7 mM concentration) and the reaction was warmed to 0 °C before being quenched, the product **2d** was isolated in 77% yield.

General Procedure for Acylation Reactions of the Dianion of Methyl Hippurate (1). To a vigorously stirred solution of MHDA (from 0.5 mmol of methyl hippurate) at −78 °C was added 1 mL of a 0.55 M THF solution of the appropriate acid chloride. The solution was stirred at −78 °C for 2 h, at which point the solution was a translucent pale yellow. The reaction was quenched at −78 °C with 10 mL of 2 N hydrochloric acid, at which point the solution became water white. The THF layer was separated from the acidic aqueous layer, which was then extracted with ether. The combined organic layers were washed with water until the aqueous washings were neutral to pH paper and then with brine. The organic layer was dried over magnesium sulfate, filtered, and concentrated at reduced pressure. The products were isolated by preparative layer chromatography.

Methyl 2-(Benzoylamido)-3-oxobutanoate (3a). Isolation was accomplished by repeated chromatgraphy (PLC, silica gel, ether followed by PLC, silica gel, ether–hexane, 9:1) to give 33 mg (28%) of **3a**: ^{1}H NMR ($CDCl_3$, 60 MHz) δ 2.48 (s, 3 H, CH_3CO), 3.84 (s, 3 H, OCH_3), 5.46 (d, 1 H, J = 6 Hz, $OCHC(N)CO_2$), 7.28–7.50 (m, 6 H, NH and aryl H's).

Methyl 2-(Benzoylamido)-3-oxopentanoate (3b). The product from the reaction of propionyl chloride and the dianion of methyl hippurate (prepared by using LHMDS) was isolated by repeated chromatography (PLC, silica gel, ether followed by PLC, silica gel, ether–hexane, 9:1) to give 60 mg (48%) of **2b**: ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.13 (t, 3 H, J = 7 Hz, $C\mathbf{H}_3CH_2$), 2.81 (t, 2 H, J = 7 Hz, $CH_3C\mathbf{H}_2$), 3.83 (s, 3 H, OCH_3), 5.45 (d, 1 H, J = 6 Hz, $OCHC(N)CO_2$), 7.26 (s, 1 H, NH), 7.36–7.55 (m, 3 H, aryl H's), 7.80–7.88 (m, 2 H, ortho aryl H's); ^{13}C NMR ($CDCl_3$) δ 7.5 (C-5), 34.4 (C-4), 53.3 (OCH_3), 62.5 (C-2), 127.3, 128.6, 132.1, 133.0, 166.9 (C-1 and CONH), 201.7 (C-3); IR (film) 3400 (NH, OH), 1750 ($C{=}O$), 1730 ($C{=}O$), 1655 cm^{-1} ($C{=}O$); mass spectrum, calcd for $C_{13}H_{15}O_4N$ *m/e* 249.1001, found *m/e* 249.1001, *m/e* (relative intensity) 249 (1), 234 (1), 218 (1), 209 (11), 208 (2), 194 (2), 193 (22), 162 (2), 161 (18), 133 (3), 121 (10), 106 (9), 105 (100), 78 (5), 77 (52), 76 (2), 59 (4), 57 (28), 51 (16).

Methyl 2-(Benzoylamido)-3-oxoheptanoate (3c). Valeryl chloride was added to MHDA prepared by using LHMDS to give, after chromatography (PLC, silica gel, ether–hexane, 9:1), 80 mg (58%) of **3c**: ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.91 (t, 3 H, J = 7 Hz, $C\mathbf{H}_3CH_2$), 1.28–1.40 (m, 2 H, $CH_3C\mathbf{H}_2$), 1.45–1.71 (m, 2 H, $C\mathbf{H}_2CH_2CO$), 2.78 (dt, 2 H, J = 7.1 Hz, J = 4.6 Hz, $CH_2C\mathbf{H}_2CO$), 3.83 (s, 3 H, OCH_3), 5.49 (d, 1 H, J = 6.5 Hz, $OCCH(N)CO_2$), 7.26 (s, 1 H, NH), 7.35–7.45 (m, 3 H, aryl H's), 7.80–7.87 (m, 2 H, ortho aryl H's); ^{13}C NMR ($CDCl_3$) δ 13.7 (C-7), 22.1 (C-6), 25.5 (C-5), 40.5 (C-4), 53.2 (OCH_3), 62.8 (C-2), 127.3, 128.6, 132.0, 133.0, 166.8 (C-1 and CONH), 200.1 (C-3); IR (film) 3350 (NH), 1745 ($C{=}O$), 1720 ($C{=}O$), 1645 cm^{-1} ($C{=}O$); mass spectrum, calcd for $C_{15}H_{19}NO_4$ *m/e* 277.1314, found *m/e* 277.1304, *m/e* (relative intensity) 277 (3), 246 (2), 208 (4), 194 (4), 193 (40), 162 (4), 161 (22), 133 (4), 121 (17), 106 (10), 105 (100), 85 (21), 78 (6), 77 (47), 76 (4), 60 (8), 59 (3), 57 (26), 51 (14).

Methyl 2-(Benzoylamido)-3-oxo-6-heptenoate (3d). (A) Small Scale. 4-Pentenoyl chloride (1.1 mmol in 1 mL of THF) was added to 1.0 mmol of MHDA prepared by using LHMDS to give, after chromatography (PLC, silica gel, ether), 200 mg (69%) of **3d**: ^{1}H NMR ($CDCl_3$, 80 MHz) δ 2.34 (m, 2 H, $H_2C{=}CHC\mathbf{H}_2$), 2.81 (m, 2 H, $CH_2C\mathbf{H}_2CO$), 3.72 (s, 3 H, OCH_3), 4.83–5.08 (m, 2 H, $CH{=}C\mathbf{H}_2$), 5.38–5.78 (m, 2 H, $OCHC(N)CO_2$ and $C\mathbf{H}{=}CH_2$), 7.26–7.48 (m, 4 H, NH and aryl H's), 7.72–7.85 (m, 2 H, ortho aryl H's); ^{13}C NMR ($CDCl_3$) δ 27.3 (C-5), 40.0 (C-4), 53.3 (OCH_3), 62.6 (C-2), 115.7 (C-7), 127.3, 128.6, 132.1, 132.9, 136.2, 168.7 and

168.8 (C-1 and CONH), 200.4 (C-3); IR (film) 3400 (NH), 1750 (C=O), 1720 (C=O), 1650 cm^{-1} (C=O); mass spectrum, calcd for $C_{10}H_{11}O_3N$ 193.0739, found *m/e* 193.0737, *m/e* (relative intensity) 216 (1), 194 (7), 193 (43), 162 (2), 161 (16), 133 (4), 121 (7), 106 (9), 105 (100), 86 (4), 84 (4), 83 (11), 78 (2), 77 (48), 76 (2), 55 (41), 51 (18).

(B) Larger Scale. 4-Pentenoyl chloride (672 mg, 5.67 mmol) was added rapidly in one portion to 5.15 mmol of MHDA (prepared by using LHMDS) in 500 mL of THF at -78 °C. The reaction was quenched after 30 min. Isolation and column chromatography (silica gel, 20% hexane in ether) gave 0.863 g (61%) of pure **3d**.

Methyl 2-(Benzoylamido)-3-oxo-3-phenylpropionate (3e). Methyl hippurate (394 mg, 2 mmol) was converted to the dianion by the standard procedure using LHMDS but under high-dilution conditions (300 mL of THF). To the stirred homogeneous solution of MHDA at -78 °C was added neat benzoyl chloride (309 mg, 2.2 mmol) in one portion. The solution was quenched and worked up as in the general procedure after 1 h at -78 °C. The product **3e** was obtained in 45% yield by trituration with hexane from chloroform: ^{1}H NMR ($CDCl_3$, 200 MHz) δ 3.72 (s, 3 H, OCH_3), 6.43 (d, 1 H, *J* = 7.3 Hz, OCC**H**(N)CO_2), 7.25 (s, 1 H, NH), 7.44–7.65 (m, 6 H, aryl H's), 7.85–7.89 (m, 2 H, aryl H's), 8.15–8.20 (m, 2 H, aryl H's); ^{13}C NMR ($CDCl_3$) δ 53.2 (OCH_3), 58.3 (C-2), 127.4, 128.6, 128.8, 129.6, 132.0, 133.1, 134.1, 134.5, 166.8, 167.3 (C-1 and CONH), 191.5 (C-3); IR (KBr) 3300 (NH), 1760 (C=O), 1695 (C=O), 1645 cm^{-1} (C=O); mass spectrum, calcd for $C_{17}H_{15}NO_4$ 297.1001, found *m/e* 297.1014, *m/e* (relative intensity) 297 (1), 238 (1), 175 (2), 162 (1), 127 (1), 126 (6), 125 (100), 78 (3), 77 (27), 76 (1), 51 (6).

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Registry No. 1, 77320-35-5; **2a** (isomer 1), 77320-36-6; **2a** (isomer 2), 77320-37-7; **2b** (isomer 1), 19185-84-3; **2b** (isomer 2), 19185-85-4; **2c** (isomer 1), 77320-38-8; **2c** (isomer 2), 77320-39-9; **2d** (isomer 1), 77320-40-2; **3a**, 77320-41-3; **3b**, 77320-42-4; **3c**, 77320-43-5; **3d**, 77320-44-6; **3e**, 19185-45-6; propionaldehyde, 123-38-6; benzaldehyde, 100-52-7; crotonaldehyde, 123-73-9; cyclohexanone, 108-94-1; CH_3COCl, 75-36-5; CH_3CH_2COCl, 79-03-8; BuCOCl, 638-29-9; CH_2=$CH(CH_2)_2COCl$, 39716-58-0; PhCOCl, 98-88-4; methyl hippurate, 1205-08-9.

Transesterification in an *O*-[(Dialkylamino)alkyl]salicylate System

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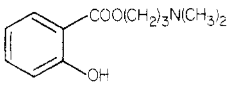
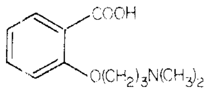
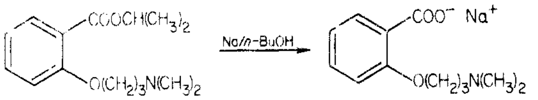
An abnormal reaction in an O-substituted salicylate system was observed in an attempt to carry out the transesterification of isopropyl *O*-[3-(dimethylamino)propyl]salicylate in butanol under basic conditions. Neither the isopropyl group nor the butyl group signal was present in the NMR spectrum of this reaction product, which was proposed to be a sodium salt of 3-(dimethylamino)propyl salicylate (1) or *O*-[3-(dimethylamino)propyl]salicylic acid (2). The possibility of the product being the sodium salt of 3-(dimethylamino)propyl salicylate (1) was ruled out by an independent synthesis of it from salicylic acid and (dimethylamino)propyl chloride.[1] The sodium salt of *O*-[3-(dimethylamino)propyl]salicylic acid (**2**) could be obtained by the hydrolysis of *O*-[3-(dimethylamino)propyl]salicylates in the presence of bases. The thus-obtained compound had the same R_f value and NMR and IR spectra as those of the previously mentioned transesterification product. Therefore, the reaction of isopropyl *O*-[3-(dimethylamino)propyl]salicylate in butanol in the presence of sodium butoxide was the sodium salt of *O*-[3-(dimethylamino)propyl]salicylic acid (**2**, eq 1).



1



2



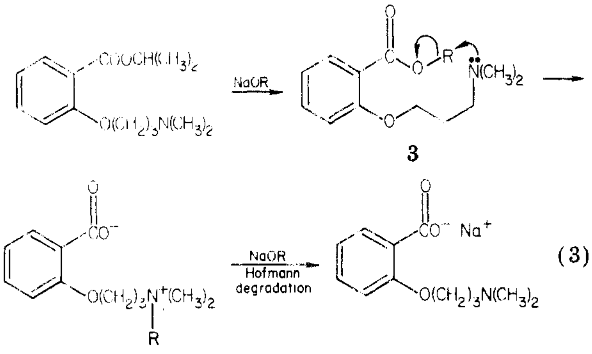
(1)

In order to check whether this unexpected product came from the hydrolysis of the salicylate, i.e., whether it was possible that the moisture in the solvent hydrolyzed the salicylate, all the solvent used was purified by dehydration of the alcohol with sodium followed by distillation. When the anhydrous solvent was used, the previously mentioned reaction had the same result as before. This indicated that the formation of *O*-[3-(dimethylamino)propyl]salicylic acid did not result from the hydrolysis of the salicylate.

It is proposed that the phenomenon observed in this work proceeds through a neighboring-group mechanism. Carboxylic esters are known to react with tertiary amine to yield quaternary ammonium salt[2] (eq 2). In our case,

$$\mathrm{RCOOMe + N(CH_3)_2(C_{12}H_{25}) \rightarrow RCOO^- \, {}^+N(CH_3)_3(C_{12}H_{25}) \rightarrow RCOOC_{12}H_{25} + N(CH_3)_3} \quad (2)$$

a carboxylic ester and tertiary amine are not only in the same molecule but also in a good relative position, which will allow the tertiary amino group to react easily with the carboxylic ester group as shown in structure **3** (eq 3).



4

(3)

The first step in this reaction is the desired transesterification. This is supported by the facts that isopropyl alcohol is detected in the distillate of the reaction mixture by GC/MS (see supplementary material) and that the transesterification product (3) is isolated under milder reaction conditions (e.g., room temperature reaction). In the presence of a base, as soon as the transesterification product is transformed into a quaternary salt intermediate (4),[2] Hofmann degradation predominates the reaction

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