1-Methyl-3-piperidone and 1-Methyl-3-pyrrolidone Derivatives from a Dieckmann Reaction

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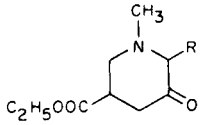
Attempts to prepare 1-methyl-5-carbethoxy-3-piperidone by a Dieckmann cyclization led to formation of its diethyl ketal on workup. The five-membered ring system, 1-methyl-4-(ethoxycarbonylmethyl)-3-pyrrolidone was also formed in the cyclization.

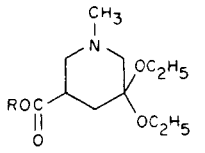
The need for 1-methyl-5-carbethoxy-3-piperidone (**1**) arose in the course of synthetic studies. The 2-methyl homolog **2** was previously prepared by Plieninger (3) *via* a Dieckmann cyclization. Following a modification of



1 R = H
2 R = CH_3

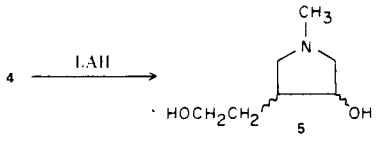
this method, outlined in Scheme 1, we obtained only a small amount of material which was later identified as **1**. Tlc analysis of the reaction products revealed that a mixture of three components had been obtained. The mixture could not be separated by fractional distillation and was purified by preparative column chromatography over silica gel. The major products isolated were identified as the diethyl ketal **3** of **1**, and the pyrrolidone ester **4**.

Ample literature precedent was found for cyclization to five-membered systems similar to **4** (4-6). Although the formation of **3** could be explained, we were surprised that it had formed, in view of the well-known difficulty in preparing such derivatives (7). More surprisingly, the ketal proved very resistant to hydrolysis. Attempts to selectively cleave the ketal led to extensive hydrolysis of the ester function. Although complete hydrolysis of the ketal by 3*N* hydrochloric acid at 40-50° took place in 2.5 hours, only 20-25% of crude material could be isolated, which had chromatographic mobility and ir and nmr spectral properties identical to **1** isolated from the reaction. Treatment of **3** with 3*N* hydrochloric acid at room temperature for 48 hours, or at *p*H 2-3 and room temperature for several days appeared to have no effect on the ketal. The relative stability of the ketal was difficult to explain and we subsequently prepared a small amount of the *n*-hexyl ester homolog **3a** of **3**. Subjecting it to similar hydrolytic conditions, *n*-hexanol was isolated in good yield. This confirmed our suspicions that ester cleavage was responsible for the low yields of **1**. Although a small percentage of non ester-cleaved piperidone was obtained, the major loss seems to result from ester hydrolysis. We are led to speculate that the 5-carboxyl function is somehow involved in the formation and relative stability of **3**. It seems possible that during the esterification of the intermediate keto acid formed in the Dieckmann reaction, anchimeric assistance from the free carboxyl may aid formation of the ketal. Once the ketal has formed and the carboxyl is esterified, steric crowding may aid in inhibiting ketal hydrolysis.

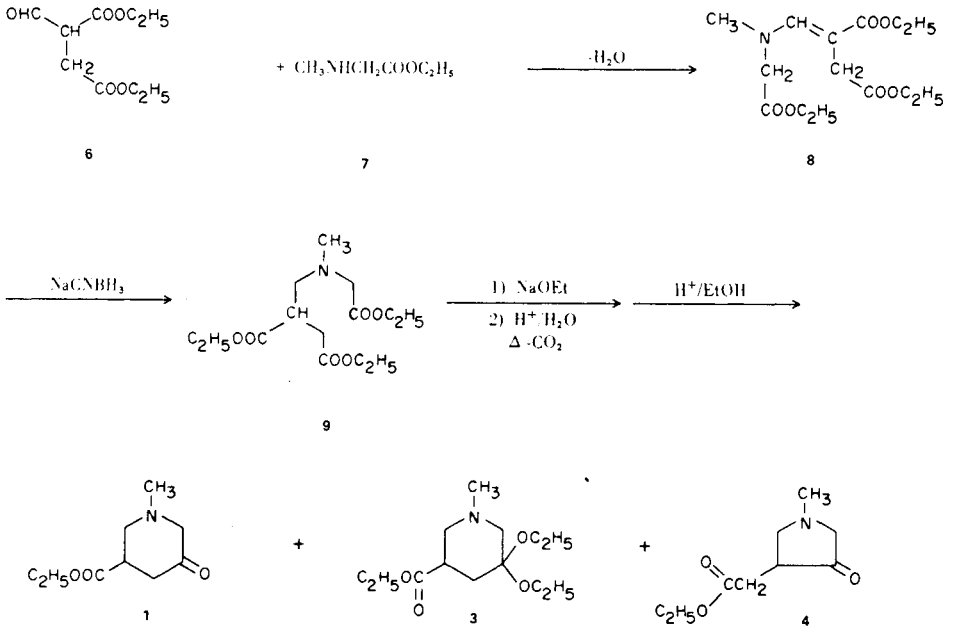


3a R = *n*-hexyl

Attempts to analyze the hydrochloride salt of **1** led to variable results. However, the mass fragmentation pattern was consistent with the proposed structure, and showed a molecular ion at m/e = 185. Mass fragmentation for **3** and **4** was also consistent with the proposed structures. The structure **4** was also confirmed by LAH reduction to the diol **5**. Both **1** and **4** required storage under nitrogen at 0° to prevent decomposition, whereas **3** was relatively stabile in air at room temperature.



Scheme I



Since Plieninger did not report similar difficulties in the preparation of **2**, it seems likely that the 2-methyl may provide sufficient steric interference to prevent ketal formation.

EXPERIMENTAL

Melting points were determined in open glass capillaries on a Thomas-Hoover Uni-Melt apparatus, and are corrected. Infrared spectra were recorded with a Beckman IR-10, and nuclear magnetic resonance spectra were recorded on a Varian Associates T-60 instrument. Elemental analyses were performed by the Microanalytical Service, College of Pharmacy, The University of Iowa, or by Midwest Microlab Ltd., Indianapolis, Indiana. Mass spectral data were obtained on a Finnigan Model 1015 mass spectrometer.

Formyl Succinate (**6**).

This was prepared from diethyl succinate and ethyl formate by the method of Wislicenus, *et al.* (8), yield 77.5%, b.p. 72°/0.4 mm. Lit. (8) b.p. 137°/15 mm.

Sarcosine Ethyl Ester (**7**).

Sarcosine ethyl ester hydrochloride was prepared from sarcosine, ethanol, and dry hydrogen chloride gas by a modification of the method of Werbin and Spoerri (9), and the free base liberated by treatment with cold potassium hydroxide solution by the method of Leonard and Barthel (10).

Ethyl [*N*-Methyl-*N*-(2,3-dicarbethoxypropen-1-yl)amino]acetate (**8**).

Following a modification of the method of Plieninger (3), 98.5 g. (0.488 mole) of formyl succinate **6** was dissolved in 200 ml. of benzene, cooled to 10-15°, and 57 g. (0.488 mole) of sarcosine ethyl ester (**7**) was added. The mixture was heated to reflux and water was continuously removed as formed. The reaction was stopped when no more water was removed, and the benzene was removed *in vacuo*. The residue was vacuum distilled, b.p. 147-149°/0.075 mm. On standing the distillate solidified and an analytical sample was recrystallized from ether-hexane, m.p. 44.5-45.5°, yield 89%.

Anal. Calcd. for $C_{14}H_{23}NO_6$: C, 55.80; H, 7.69; N, 4.64. Found: C, 55.61; H, 7.90; N, 4.52.

Ethyl [*N*-Methyl-*N*-(2,3-dicarbethoxypropyl)amino]acetate (**9**).

Following a modification of the method of Borch, *et al.* (11), 30.1 g. (0.1 mole) of the enamine **8** was dissolved in 200 ml. of absolute ethanol. Sodium cyanoborohydride (Alfa Inorganics) 6.46 g. (0.103 mole) was added all at once, and the *p*H was monitored with *p*H paper and maintained at 3-4 by addition of 2*N* ethanolic-hydrogen chloride. Tlc analysis indicated reaction completeness after one hour. The reaction mixture was concentrated *in vacuo*, the residue dissolved in one liter of cold water, made basic by addition of solid potassium carbonate, and the solution extracted with 4 x 400 ml. of ether. The ether extracts were dried (sodium sulfate), concentrated, and the residual oil was vacuum distilled, b.p. 128-130°/0.6 mm, yield 29.1 g. (96%).

Anal. Calcd. for $C_{14}H_{25}NO_6$: C, 55.50; H, 8.25; N, 4.62. Found: C, 55.57; H, 8.52; N, 4.40.

Dieckmann Cyclization and Separation of Products.

Following the procedure of Plieninger (3), 3.53 g. (0.153 mole) of sodium metal was dissolved in 80 ml. of dry ethanol. Toluene, 200 ml., was added and the ethanol was removed by azeotropic distillation. Additional toluene was added to maintain the volume. A solution of 30.3 g. (0.1 mole) of triester **9** in 60 ml. of toluene was added slowly and the ethanol removed as its toluene azeotrope. The mixture was heated to reflux for two hours, cooled, and 40 ml. of concentrated hydrochloric acid was added. The mixture was heated at reflux with vigorous stirring for 48 hours, at which time an aliquot of the aqueous layer no longer gave a positive ferric chloride test. The reaction mixture was cooled and concentrated under reduced pressure. The residual mass was taken up in 200 ml. of ethanol and the solvent distilled *in vacuo*. The process was repeated several times to

remove all traces of water. Finally, the viscous brown residue was dissolved in 400 ml. of dry ethanol, saturated with hydrogen chloride gas, and allowed to stir at room temperature for 48 hours. The mixture was concentrated, the residue was dissolved in cold water, and neutralized with solid potassium carbonate. The free base was dissolved in ether, the ether extracts dried (sodium sulfate), concentrated, and the residual oil vacuum distilled, b.p. 125-135°/10-12 mm, yield 15.4 g. Tlc (silica gel-ether) showed three major components with R_f = 0.20, 0.35, and 0.55 plus a minor component with R_f = 0.47.

A 50 x 1,000 mm column was packed with 650 g. of degassed silica gel (J. T. Baker, 60-200 mesh) in ether. Seventeen g. of cyclization product mixture was applied to the column and eluted with ether. An 82% recovery of material was obtained from the column. The individual major components were identified and their physical properties and yields obtained in the effluent are given below.

Ethyl 1-Methyl-5,5-diethoxypiperidine-3-carboxylate (**3**).

This was the first fraction eluted from the column, yield 8.45 g. (60.5% of the eluted material), R_f = 0.55 (tlc, silica gel-ether); purified by vacuum distillation, b.p. 140-142°/9-11 mm; ir (neat) 1732 cm^{-1}; nmr (deuteriochloroform) δ: 1.15 (t, 3H, $-CH_3$), 1.20 (t, 3H, $-CH_3$), 1.23 (t, 3H, $-CH_3$), 1.61-3.20 (m, 7H, CH, CH_2), 2.33 (s, 3H, NCH_3), 3.50 (q, 2H, O-CH_2-ether), 3.57 (q, 2H, O-CH_2-ether), 4.15 (q, 2H, O-CH_2-ester). The hydrochloride salt was prepared for elemental analysis, m.p. 138-138.5° (ethanol-ether).

Anal. Calcd. for $C_{13}H_{26}ClNO_4$: C, 52.78; H, 8.86; N, 4.73. Found: C, 53.17; H, 9.03; N, 5.06.

1-Methyl-4-(ethoxycarbonylmethyl)-3-pyrrolidone (**4**).

This was the third fraction eluted from the column, 4.55 g. (32.5%); R_f = 0.20; ir (neat) 1732 cm^{-1} and 1760 cm^{-1}; nmr (deuteriochloroform) δ: 1.25 (t, 3H, $-CH_3$), 2.23-3.15 (m, 5H, CH, CH_2), 3.24-3.52 (m, 2H, CH_2), 2.47 (s, 3H, NCH_3), 4.15 (q, 2H, O-CH_2-).

Anal. Calcd. for $C_9H_{15}NO_3$: C, 58.36; H, 8.16; N, 7.56; O, 25.91. Found: C, 58.41; H, 8.12; N, 7.17; O, 25.84.

1-Methyl-5-carbethoxy-3-piperidone (**1**).

This was the second fraction eluted from the column, 1.0 g. (7%); R_f = 0.35; ir (neat) 1732 cm^{-1}; nmr (deuteriochloroform) δ: 1.27 (t, 3H, $-CH_3$), 2.36 (s, 3H, NCH_3), 2.44-3.33 (m, 7H, CH, CH_2), 4.20 (q, 2H, O-CH_2-ester). Mass spectrometry (70 eV) showed a molecular ion at m/e = 185 and the fragmentation pattern was consistent with the proposed structure. The hydrochloride was prepared m.p. 96-97° dec., but consistent values could not be obtained for elemental composition.

1-Methyl-4-(2-hydroxyethyl)-3-pyrrolidinol (**5**).

To a stirring suspension of 558 mg. (0.02 mole) of LAH in 50 ml. of dry ether was added 0.01 mole of **4**. The mixture was refluxed with stirring for 4 hours and then cooled and carefully decomposed with 5 ml. of water. The alumina was removed by filtration and extracted with chloroform. The chloroform washes were combined with the ether filtrate and the solution was dried (sodium sulfate), and the solvent removed under reduced pressure. The residue was vacuum distilled, b.p. 109-110°/0.1 mm. The distillate was obtained as an extremely viscous colorless oil, yield 700 mg. (53.4%) of *erythro-threo* mixture. The nmr spectrum (deuteriochloroform) showed a triplet at δ 3.53 for the deshielded methylene next to the side chain hydroxyl and split by the adjacent methylene protons.

Anal. Calcd. for $C_7H_{15}NO_2$: C, 57.90; H, 10.41; N, 9.65. Found: C, 58.25; H, 10.03; N, 9.69.

Hexyl 1-Methyl-5,5-diethoxypiperidine-3-carboxylate (**3a**).

To a solution of 8.4 g. (3.24 millimoles) of ester ketal **3** in 50 ml. of dry 1-hexanol was added 100 mg. of sodium metal. The sodium slowly dissolved and the mixture was stirred at room temperature under a vacuum of 50-80 mm Hg for 48 hours. The hexanol was removed *in vacuo* and the residue vacuum distilled, b.p. 115-117°/0.15 mm, yield 8.65 g. (85%).

Anal. Calcd. for $C_{17}H_{33}NO_4$: C, 64.72; H, 10.54; N, 4.44; O, 20.28. Found: C, 64.95; H, 10.41; N, 4.29; O, 20.46.

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