

Derivatives of 1-Azabicyclo[4.3.1]decane

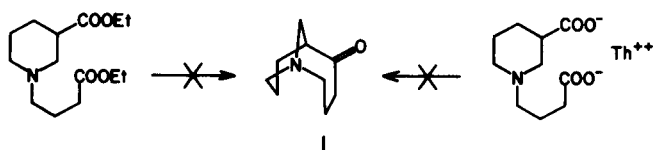
Charles F. Hammer and John H. Craig

Department of Chemistry, Georgetown University, Washington, D. C. 20007

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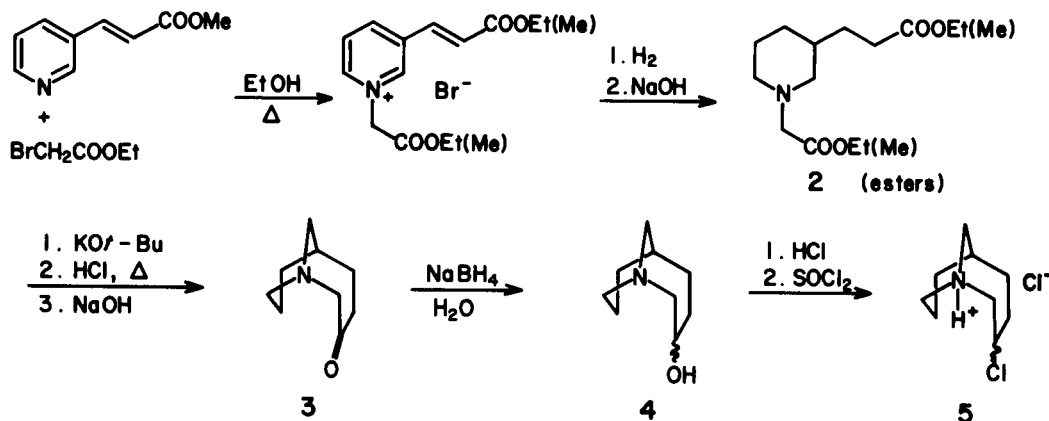
1-Azabicyclo[4.3.1]decan-3-one has been synthesized *via* Dieckmann condensation and converted to the corresponding hydroxy and chloro derivatives.

Synthesis of the 1-azabicyclo[4.3.1]decane ring system does not appear in the literature. Clemo (1) reported unsuccessful attempts to prepare the 4-keto derivative (1) *via* Dieckmann cyclization and *via* pyrolysis of a thorium salt. However, this evidence should not be used to conclude that a Dieckmann cyclization would not work for the synthesis of 1-azabicyclo[4.3.1]decane ring systems, because he also reported these same methods to be unsuccessful for the smaller homolog, 1-azabicyclo[3.3.1]nonan-4-one,



which McElvain and Adams (2) had prepared earlier by the Dieckmann method. Also, Leonard (3) has used the Dieckmann condensation to prepare a similar ring system (11-methyl-11-azabicyclo[3.3.1]undecan-4-one) where a larger 8-membered ring was formed by closing the 5-carbon bridge.

The reaction scheme below shows the approach taken here for synthesizing the 1-azabicyclo[4.3.1]decane ring system *via* Dieckmann condensation:



Commercially available methyl β -(3-pyridyl)acrylate, in ethanol was alkylated with ethyl bromoacetate and hydrogenated over 5% rhodium on alumina. A mixture of the mixed methyl and ethyl esters of diacid 2 was obtained upon workup, extensive alkoxy exchange having occurred between the ester groups and the ethanol solvent. The diester mixture was cyclized with potassium *t*-butoxide in refluxing xylene under the high-dilution conditions of Leonard and Sentz (4) over a period of 48 hours. After decarboxylation and workup, a reddish oil was obtained from which a small amount of crude amino ketone (3) was sublimed. Resublimation gave an 8% yield of pure product which was unstable at room temperature. Attempts to obtain a stable hydrochloride of 3 failed.

The physical characteristics of 3 (e.g., facile sublimation) were similar to those of other bicyclic α -amino ketones. The instability of 3 ruled out elemental analysis. The ir spectrum showed the presence of a carbonyl group (1696 cm^{-1}) and the absence of a C-O-C ester stretching vibration. The pmr spectrum showed an absorption for the methylene group between the carbonyl group and the nitrogen atom ($\delta 3.5$). The correct *m/e* ratio was established from the parent peak at mass 153 in the mass spectrum. This was consistent with the correct empirical formula of $\text{C}_9\text{H}_{15}\text{NO}$. A theoretical calculation of the relative inten-

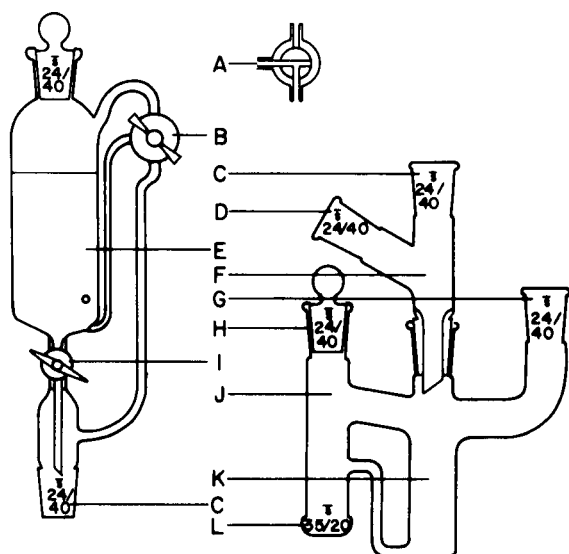


Figure 1. Apparatus for Synthesizing 1-Azabicyclo[4.3.1]-decan-3-one (3): A, three-way stopcock in position for constant rate of addition; B, three-way stopcock; C, connection between dropping funnel and "T" adapter; D, position of nitrogen inlet tube after formation of KOt-Bu ; E, constant-addition-rate dropping funnel; F, "T" adapter (rotated 90° from position shown); G, position for attachment of distilling head; H, position for addition of potassium; I, Kontes variable-bore stopcock; J, high dilution apparatus; K, dilution chamber; L, ball joint leading to the reaction vessel *via* an adapter.

sities of the peaks surrounding the parent peak due to naturally occurring isotopes was performed. This involved the use of a computer program developed by Hammer and Vlietstra (5), in which corrections are made for contributions from P-1 and P-2 peaks. A good fit was obtained with the observed peaks for this empirical formula.

The low yield in this cyclization reaction was probably due to low cyclization efficiency of this particular intermediate ring system. However, there was also a considerable loss of the α -aminoketone actually formed due to decomposition during isolation.

Compound **3** was reduced to the corresponding β -amino alcohol (**4**) with aqueous sodium borohydride (6) and isolated in 81% yield by vacuum sublimation. The ir spectrum showed the presence of a hydroxyl group (3400 and 2700 cm^{-1}). The pmr spectrum showed a broad band for a single proton α to a hydroxyl group ($\delta 4.4$ to 3.6). A glc examination revealed two peaks (neither of which was the α -amino ketone) in a ratio of 85 to 15. The flexibility of this bicyclic ring makes it difficult to decide on the conformation in which, one would expect the reaction

of the carbonyl group with hydride to occur. Hence specific *endo* and *exo* assignments have not been made for the epimeric mixture of amino alcohols.

A 50% increase in the amount of amino alcohol obtained was achieved by treating the glass residue from re-sublimation of crude **3** with sodium borohydride. Hence it is possible that a significant increase in the overall cyclization yield can be obtained if the crude ketone is reduced directly to the amino alcohol without isolation. An approximate corrected yield of 11% was calculated for **3** based on the additional **4** recovered from the resublimation residue.

Compound **4** was converted to the β -chloro amine salt (**5**) by treating the hydrochloride of **4** in chloroform with thionyl chloride. An ir spectrum of the product showed the presence of a tertiary ammonium band (2500 cm^{-1}), but the C-Cl band could not be identified due to the large number of sharp ir absorptions below 1000 cm^{-1} , presumably due to the skeletal vibrations of the bicyclic ring. The pmr spectrum contained a broad band between $\delta 5.1$ and 4.3 , characteristic of a ring proton adjacent to a chlorine atom.

Several useful modifications of the high dilution apparatus for the Dieckmann condensation (4) are shown in Figure 1. The flattened bottom of the dilution chamber permits magnetic stirring as desired and the third neck facilitates addition of potassium. The constant-addition-rate dropping funnel with a Kontes variable-bore stopcock gives good control over delivery rates of diester solution with little tendency toward clogging.

EXPERIMENTAL (7)

Mixed Diesters (Methyl and Ethyl) of 3-(β -Carboxyethyl)-1-(carboxymethyl)piperidine (**2**).

A mixture of methyl β -(3-pyridyl)acrylate (32.6 g., 0.200 mole) and ethyl bromoacetate (34.1 g., 0.204 mole) in absolute ethanol (100 ml.) was warmed at 35° for four days, then diluted to 250 ml. with more ethanol and hydrogenated over 5% rhodium on alumina (5 g.) at 40° and 4 atmospheres until uptake of hydrogen ceased (8 hours). After filtering off the catalyst, most of the ethanol was removed from the filtrate *in vacuo*, giving a dark brown oil. The combined products from the above reaction sequence, performed three times, were dissolved in water (50 ml.), overlaid with ether (100 ml.), and neutralized (while cooling in an ice bath) with 50% aqueous sodium hydroxide. The ether phase was separated and the aqueous phase further extracted with ether (4 x 50 ml.) and the combined ether extracts dried (sodium sulfate) and the ether removed *in vacuo*. The remaining reddish oil was vacuum distilled, giving the product as a clear oil: 112 g., 0.42 mole, 70% based on 0.600 mole of methyl β -(3-pyridyl)acrylate and an 85 to 15 ethoxy to methoxy composition as assigned from pmr spectra, b.p. $123\text{--}124^\circ$ (0.3 mm); n_D^{20} 1.4630; ir (liquid film) 1743 (C=O) and 1170 cm^{-1} (C-O-C); pmr (carbon tetrachloride with TMS) $\delta 4.08$ and 4.05 (two overlapping q, 3.3, $J = 7\text{ Hz}$, OCH_2CH_3), 3.62 and 3.59 (two s, 0.9, OCH_3), 3.09 (s, 2, $\text{NCH}_2\text{-COOR}$), and 3.0 to 0.7 ppm (broad overlapping bands for all re-

maining hydrogens, including two overlapping at δ 1.24 and 1.22, $J = 7$ Hz, OCH_2CH_3).

1-Azabicyclo[4.3.1]decan-3-one (3).

Anhydrous xylene (2000 ml.) was placed in a 3-neck, round-bottomed flask equipped with a pressure-equalizing dropping funnel (topped with a nitrogen inlet tube), a Trubore stirrer, and a 3-neck, high dilution apparatus (4) fitted with a constant-addition-rate dropping funnel and distillation head (Figure 1). The reaction was conducted under a slow stream of dry nitrogen. After purging, freshly trimmed potassium (45.6 g., 1.17 moles) was added and the molten metal finely pulverized by vigorous stirring under gentle reflux. Then *t*-butyl alcohol (118 g., 1.6 moles) was cautiously added through the dropping funnel to the vigorously stirred refluxing mixture over 1.5 hours. Refluxing was continued for an additional 0.5 hour until all of the potassium was consumed. Excess *t*-butyl alcohol was removed as an alcohol-xylene azeotrope (300 ml.). Then, after the nitrogen inlet tube was transferred to the high-dilution apparatus, a solution of the mixed methyl and ethyl esters of **2** (110 g., 0.41 mole) in dry xylene (1000 ml.) was added to the vigorously stirred, gently refluxing reaction mixture over 48 hours, while alcohol-xylene distillate was removed continuously at a rate approximately equal to the rate of addition of diester solution. Afterwards, the bright orange mixture was stirred under reflux for an additional 2 hours while alcohol-xylene distillate removal was continued. The stirred reaction mixture was then cooled in an ice bath and acidified by slowly adding 6*N* hydrochloric acid. The xylene layer was separated and further extracted with 6*N* hydrochloric acid (3 x 200 ml.). The combined acid extracts were refluxed for 10 hours and then concentrated *in vacuo*. The semisolid residue was overlaid with hexane (300 ml.) and made strongly basic with excess 50% aqueous sodium hydroxide. Then anhydrous potassium carbonate (30 g.) was added while shaking vigorously. The hexane layer was decanted and the semisolid residue further extracted with hexane (3 x 200 ml.). The combined hexane extracts were dried (potassium carbonate) and the solvent removed *in vacuo*. Vacuum sublimation of the remaining reddish oil at 100° and 0.1 mm gave an 8.1 g. yield of crude product which was resublimed at 78° and 0.1 mm giving **3** as a clear, waxy hygroscopic solid: 4.9 g., 0.032 mole, (7.9%); *ir* (potassium bromide disc) 1696 cm^{-1} (C=O); *pmr* (deuteriochloroform with TMS) δ 3.9 to 3.0 (*A* and *B* portions of *AB* coupling system, 2, $J_{AB} = 16$ Hz, NCH_2CO), 3.5 to 2.3 ($\text{CH}_2\text{CH}_2\text{CH}_2\text{N}(\text{CH}_2\text{CH})\text{CH}_2\text{COCH}_2\text{CH}_2$) and 2.3 to 0.9 ppm ($\text{CH}_2\text{CH}_2\text{CH}_2\text{N}(\text{CH}_2\text{CH})\text{CH}_2\text{COCH}_2\text{CH}_2$); *ms* (8) (70eV) *m/e* (relative intensity) 115 (1), 154 (7), 153 (59), 152 (2), 151 (2), 126 (7), 125 (59), 124 (66), 110 (17), 98 (6), 97 (85), 96 (100), 84 (9), 83 (36), 82 (18), 70 (9), 69 (43), 68 (14), 67 (10), 58 (11), 57 (9), 56 (10), 55 (19), 54 (7), 53 (7), 43 (42), 42 (55), 41 (38), 39 (15), [155 (P+2, 2.0), 154 (P+1, 12.4), 153 (P, 100), 152 (P-1, 3.2), 151 (P-2, 3.3)]; calculated for $\text{C}_9\text{H}_{15}\text{NO}$, *m/e* 155 (P+2, 0.72), 154 (P+1, 10.72), 153 (P, 100), 152 (P-1, 3.2), 151 (P-2, 3.3)].

The instability of **3** reduced yields upon purification and rendered the product unsuitable for an elemental analysis or for a melting point determination. A sample of **3** was dissolved in benzene and converted to the hydrochloride by bubbling in anhydrous hydrogen chloride. The hydrochloride oiled out of the benzene and remained an oil upon attempted recrystallization from a variety of solvents.

3-Hydroxy-1-azabicyclo[4.3.1]decane (4).

A solution of **3** (3.5 g., 0.023 mole) in water (6 ml.) was added over 15 minutes to a stirred solution of sodium borohydride (0.50

g., 0.013 mole) in water (10 ml.). The reaction solution was allowed to stand overnight, and then was cooled in an ice bath, cautiously acidified to a Congo Red endpoint with concentrated hydrochloric acid, and concentrated to a thick syrup *in vacuo*. The residue was overlaid with ether (50 ml.) and made basic with 50% aqueous sodium hydroxide (15 ml.) while shaking vigorously. The ether was decanted and the residue further extracted with ether (3 x 50 ml.). The combined ether extracts were dried (potassium carbonate) and the ether removed *in vacuo*. The solid residue was sublimed at 100° and 0.08 mm, giving **4** as a clear, waxy solid: 2.9 g., 0.019 mole, 81%, m.p. 83-95°; *ir* (potassium bromide disc) 3400 and 2700 (broad O-H, the latter band internally hydrogen bonded) and 1040 cm^{-1} (C-O); *pmr* (deuteriochloroform with TMS) δ 4.2 (s, 1, OH), 4.4 to 3.6 (broad band, 1, >CHOH), 3.6 to 2.3 (broad band, 6, $\text{CH}_2\text{CH}_2\text{CH}_2\text{N}(\text{CH}_2\text{CH})\text{CH}_2\text{CHOHCH}_2\text{CH}_2$), and 2.3 to 1.0 ppm (broad band, 9, $\text{CH}_2\text{CH}_2\text{CHN}(\text{CH}_2\text{CH})\text{CH}_2\text{CHOHCH}_2\text{CH}_2$); *glc* (Carbowax column, 200°, 88 ml/min He) 8.3 and 8.7 min (isomers of **4**, 85 and 15% respectively).

Anal. Calcd. for $\text{C}_9\text{H}_{17}\text{NO}$: C, 69.63; H, 11.04; N, 9.03. Found: C, 69.67; H, 11.14; N, 9.11.

The resublimation residue from the preparation of **3** was treated with sodium borohydride in precisely the same manner and quantities as described above for the preparation of **4**. Additional sublimed **4** was obtained: 1.5 g., m.p. 82-84°.

3-Chloro-1-azabicyclo[4.3.1]decane Hydrochloride (5).

Compound **4** (3.5 g., 0.023 mole) in chloroform (50 ml.) was converted to the hydrochloride by bubbling in anhydrous hydrogen chloride. Traces of moisture were removed by distilling off some of the chloroform (25 ml.). After cooling, a solution of thionyl chloride (4.0 g., 0.034 mole) in chloroform was added over 10 minutes to the stirred amino alcohol hydrochloride solution and the reaction mixture refluxed for 4 hours. Excess thionyl and chloroform were removed *in vacuo* and residual thionyl destroyed by adding methanol which was then removed *in vacuo*. The residue was dissolved in water, decolorized twice (Nuchar C-190N), and the water removed *in vacuo*. The residue was recrystallized from acetone-ethanol, giving **5**: 1.6 g., 0.0076 mole, 34%, m.p. 150-153°; *ir* (potassium disc) 2500 cm^{-1} (broad tertiary N^+H); *pmr* (deuterium oxide-concentrated hydrochloric acid with Tiers' salt) δ 5.1 to 4.3 (broad band, 1, >CHCl), 4.3 to 2.8 (broad band, 6, $\text{CH}_2\text{CH}_2\text{CH}_2\text{N}(\text{CH}_2\text{CH})\text{CH}_2\text{CHClCH}_2\text{CH}_2$) and 2.8 to 1.0 ppm (broad overlapping bands, 9, $\text{CH}_2\text{CH}_2\text{CH}_2\text{N}(\text{CH}_2\text{CH})\text{CH}_2\text{CHClCH}_2\text{CH}_2$).

Anal. Calcd. for $\text{C}_9\text{H}_{17}\text{Cl}_2\text{N}$: C, 51.44; H, 8.15; Cl, 33.74; N, 6.66. Found: C, 51.53; H, 8.23; Cl, 33.90; N, 6.44.

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(7) Melting points were taken in capillary tubes and are corrected. Boiling points are uncorrected. Ir spectra were recorded on a Perkin-Elmer 225 infrared spectrophotometer and pmr spectra on a Varian Associates A-60 spectrometer. Tetramethylsilane (TMS) and sodium 3-(trimethylsilyl)-1-propanesulfonate (Tiers' salt) were used as internal pmr standards. Mass

spectra were determined on an Associated Electrical Industries, Ltd., MS-1201 mass spectrometer and glc data were obtained on a Barber-Colman Series 5000 gas chromatograph with a flame ionization detector. The carrier gas was helium and the column was 244 cm by 6.4 mm O.D. stainless steel containing 13% Carbowax 20M on 90/100 mesh Anakrom ABS. Elemental analyses were performed by Organic Microanalyses, 5757 Decelles Ave., Montreal, Quebec, Canada.

(8) An underline indicates intensities (%) relative to the parent peak (P).