# Cyclic β-Enamino Esters Dialkylation: A New Route to Cyclic Imines



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The bis-alkylation of cyclic β-enamino esters has been investigated, and exploited as a general method of synthesis of cyclic monosubstituted imines.

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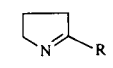
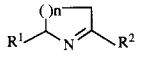
A number of alkaloids from ant venoms have a common structural moiety in the 2-alkyl-Δ-1-pyrroline **1**, or in the 2-alkyl-Δ-1-piperideine **2** skeletal unit. Among others, specific examples include 2,5-dialkyl-Δ-1-pyrrolines **3** (n = 1) [1], and 2,6-dialkyl-Δ-1-piperideines **3** (n = 2) [1] which are produced by ants in the genera *Monomorium* and *Solenopsis*, respectively. Monosubstituted derivatives **3** (n = 1, 2, 3, $R^1$ = H) are also interesting for their insecticidal activities, and for their synthetic potential [2].



**1**
R = alkyl or alkenyl

**2**
R = alkyl or alkenyl



**3** (n=1,2,3)
$R^1$ = H, alkyl, or alkenyl
$R^2$ = Alkyl, or alkenyl

We were intrigued by the possibility of preparing various cyclic imines **3** bearing a functionalized substituent. These derivatives can be prepared by cyclization reactions [3], by intramolecular rearrangements [4], or by chemical transformations of a lactam precursor [5], but only a few of theses syntheses can be extended to functionalized substituents.

In connection with our work on the use of cyclic β-enamino esters in heterocyclic synthesis, we report herein a general methodology for the preparation of gem-disubstituted cyclic β-imino esters **5** by the bis-alkylation of β-enamino esters.

In previous work we have demonstrated that the regio and stereospecific *C*-alkylation of β-enamino esters **4** depends on the size of the heterocycle. For seven membered ring compounds, a direct alkylation can be obtained by heating **4** with alkyl halides, but with smaller rings, a strong basic medium is necessary to lead to mono-alkylated β-enamino esters **6** [6].

β-Enamino esters **4** can be transformed into bis-alkylated β-imino esters **5** (n = 1, 2, 3, R = R' = alkyl) either in one or two reaction steps according to the nature of the substituent.

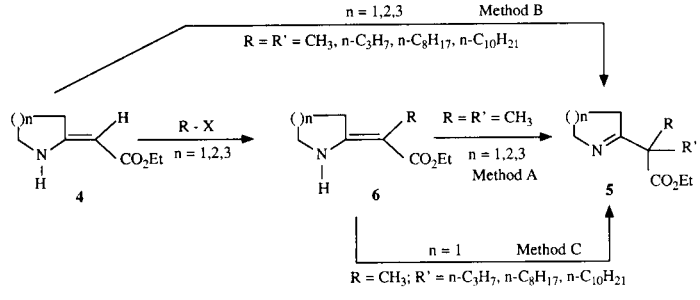
A mild alkylation of compounds **6** (heating in a halide without solvent) permits us to prepare β-imino esters **5** (n = 1, 2, 3, R = $CH_3$) but this reaction is limited to gem-dimethyl substituents (Method A). When another halide is used instead of methyl iodide the reaction is always incomplete.

Meanwhile, a direct bis-alkylation of β-enamino esters **4** can be achieved when heating an excess of halide (4.4 equivalents) with the sodium salts of compounds **4** (Method B). These conditions permit easy access to gem-dialkyl β-imino esters **5** but are not appropriate to the synthesis of unsymmetrical gem-disubstituted compounds.

**Table 1**

**β-Enamino Esters Bis-alkylation**

| n | R | R' | Method | Yield % |
|---|---|---|---|---|
| 1 | $CH_3$ | $CH_3$ | A | 79 |
| | $CH_3$ | $CH_3$ | B | 48 |
| | *n*-$C_3H_7$ | *n*-$C_3H_7$ | B | 74 |
| | *n*-$C_8H_{17}$ | *n*-$C_8H_{17}$ | B | 40 |
| | *n*-$C_{10}H_{21}$ | *n*-$C_{10}H_{21}$ | B | 52 |
| | $CH_3$ | *n*-$C_3H_7$ | C | 56 |
| | $CH_3$ | *n*-$C_8H_{17}$ | C | 24 |
| | $CH_3$ | *n*-$C_{10}H_{21}$ | C | 12 |
| 2 | $CH_3$ | $CH_3$ | A | 60 |
| | $CH_3$ | $CH_3$ | B | 58 |
| | *n*-$C_3H_7$ | *n*-$C_3H_7$ | B | 56 |
| | *n*-$C_8H_{17}$ | *n*-$C_8H_{17}$ | B | 61 |
| | *n*-$C_{10}H_{21}$ | *n*-$C_{10}H_{21}$ | B | 33 |
| 3 | $CH_3$ | $CH_3$ | A | 65 |
| | $CH_3$ | $CH_3$ | B | 30 |



Nevertheless monoalkylated β-enamino esters **6** react with many alkyl halides in drastic basic conditions to lead to unsymmetrical derivatives **5** (Method C). Results are summarized in Table 1.

In conclusion, various α,α'-bis-alkylated cyclic β-imino esters can be prepared from cyclic β-enamino esters but reaction conditions depend on the nature of the alkyl substituents.

## EXPERIMENTAL

All melting points were determined with a Büchi apparatus and are uncorrected. The ir spectra were recorded on a Philips PU 9700 spectrometer. The $^1H$ nmr and $^{13}C$ nmr spectra were measured with a Bruker WP 80 (80 MHz), and Bruker AC 200 (200 MHz). The $^1H$ nmr chemical shifts are reported in ppm from an internal standard TMS, or of residual chloroform. The $^{13}C$ nmr chemical shifts are reported in ppm from the central peak of deuteriochloroform (77.1 ppm). Analytical tlc was performed on Merck precoated silica gel 60F plates. Merck silica gel 60 (230-400 mesh) was used for column chromatography.

Alkylation of Cyclic Mono-alkyl β-Enamino Esters **6** (Method A).

Mono-alkyl β-enamino ester **6** (0.02 mole) is heated in 50 ml of methyl iodide for 12 hours. The excess halide is evaporated under reduced pressure then the residue is treated with 30 ml of a saturated aqueous solution of potassium carbonate. The solution is extracted with chloroform (3 x 30 ml) and the organic layer is dried over sodium sulfate. Solvent is evaporated under reduced pressure and the crude oil is distilled under vacuum.

Direct Bis-alkylation of Cyclic β-Enamino Esters **4** (Method B).

β-Enamino ester **4** (0.02 mole) is added to a suspension of sodium hydride (0.044 mole, 1.05 g) in toluene (50 ml) and the solution is refluxed 1 hour. After cooling, halide (4 equivalents) in 15 ml of toluene is added dropwise and the mixture is refluxed for 12 hours. Water is added (50 ml) and the aqueous layer is separated, neutralized with a 10% aqueous solution of hydrochloric acid, then extracted with chloroform (3 x 30 ml). The combined organic layers are dried over sodium sulfate and the solvents are evaporated under reduced pressure. Crude products are then distilled under vacuum.

Unsymmetrical gem-Dialkyl Cyclic β-Imino Esters **5** Preparation (Method C).

Mono-alkyl β-enamino ester **6** (0.02 mole) is heated 1 hour with a suspension of 0.022 mole of sodium hydride (1.1 equivalents) in toluene (50 ml). After cooling, halide (2 equivalents) in toluene (15 ml) is then added dropwise and the mixture is refluxed for 12 hours. Workup is identical with method B.

Ethyl 2-[2-(3,4-Dihydro-5*H*-pyrrolyl]-2-methylpropanoate (**5**) (n = 1, R = R' = $CH_3$) (Methods A or B).

This compound was obtained in a yield of 79% (A) or 48% (B), bp 64°/0.07 Torr; ir (neat): ν 1725, 1640 $cm^{-1}$; $^1H$ nmr (deuteriochloroform): δ 1.20 (t, 3H, J = 7.1 Hz), 1.38 (s, 6H), 1.85 (qt, 2H, J = 7 Hz), 2.45-2.55 (m, 2H), 3.75-3.85 (m, 2H), 4.1 (q, 2H, J = 7.1 Hz); $^{13}C$ nmr (deuteriochloroform): δ 14.1, 23.0, 23.7, 34.3, 47.2, 60.7, 61.0, 175.0, 179.1.

*Anal.* Calcd. for $C_{10}H_{17}NO_2$: C, 65.54; H, 9.35; N, 7.64. Found: C, 65.72; H, 9.14; N, 7.48.

Ethyl 2-[2-(3,4-Dihydro-5*H*-pyrrolyl]-2-propylpentanoate (**5**) (n = 1, R = R' = $n$-$C_3H_7$) (Method B).

This compound was obtained in a yield of 74%, bp 175°/1 Torr; ir (neat): ν 1720, 1625 $cm^{-1}$; $^1H$ nmr (deuteriochloroform): δ 0.88 (t, 6H, J = 7.1 Hz), 1.02-1.20 (m, 4H), 1.22 (t, 3H, J = 7 Hz), 1.70-2.00 (m, 6H), 2.32-2.48 (m, 2H), 3.78-3.88 (m, 2H), 4.13 (q, 2H, J = 7.1 Hz); $^{13}C$ nmr (deuteriochloroform): δ 14.0, 14.3, 17.1, 22.6, 34.7, 34.9, 54.5, 60.3, 60.4, 173.8, 177.6.

*Anal.* Calcd. for $C_{14}H_{25}NO_2$: C, 70.25; H, 10.53; N, 5.85. Found: C, 70.08; H, 10.48; N, 6.06.

Ethyl 2-[2-(3,4-Dihydro-5*H*-pyrrolyl]-2-octyldecanoate (**5**) (n = 1, R = R' = $n$-$C_8H_{17}$) (Method B).

This compound was obtained in a yield of 40%, bp 60°/0.05 Torr; ir (neat): ν 1725, 1625 $cm^{-1}$; $^1H$ nmr (deuteriochloroform): δ 0.7-0.9 (m, 6H), 1.00-1.35 (m, 27H), 1.60-2.00 (m, 6H), 2.30-2.40 (m, 2H), 3.70-3.90 (m, 2H), 4.12 (q, 2H, J = 7.1 Hz); $^{13}C$ nmr (deuteriochloroform): δ 13.9, 14.0, 14.2, 22.7, 23.9, 29.4, 29.5, 30.0, 32.0, 32.4, 35.1, 54.8, 60.6, 60.7, 174.2, 178.0.

*Anal.* Calcd. for $C_{24}H_{45}NO_2$: C, 75.93; H, 11.95; N, 3.69. Found: C, 76.10; H, 11.73; N, 3.61.

Ethyl 2-[2-(3,4-Dihydro-5*H*-pyrrolyl]-2-decyldodecanoate (**5**) (n = 1, R = R' = $n$-$C_{10}H_{21}$) (Method B).

This compound was obtained in a yield of 52%, bp 200°/0.1 Torr; ir (neat): ν 1725, 1640; $^1H$ nmr (deuteriochloroform): δ 0.95 (t, 3H, J = 6.9 Hz), 1.03-1.40 (m, 36H), 1.73-2.05 (m, 8H), 2.28-2.57 (m, 2H), 3.70-3.90 (m, 2H), 4.22 (q, 2H, J = 7 Hz); $^{13}C$ nmr (deuteriochloroform): δ 14.0, 14.1, 22.6, 24.0, 29.3, 29.6, 30.0, 31.9, 32.4, 35.0, 40.0, 54.7, 60.8, 61.0, 174.0, 177.9.

*Anal.* Calcd. for $C_{28}H_{53}NO_2$: C, 77.18; H, 12.26; N, 3.21. Found: C, 77.52; H, 12.04; N, 3.37.

Ethyl 2-[2-(3,4-Dihydro-5*H*-pyrrolyl]-2-methylpentanoate (**5**) (n = 1, R = $n$-$C_3H_7$, R' = $CH_3$) (Method C).

This compound was obtained in a yield of 56%, bp 80°/0.08 Torr; ir (neat): ν 1725, 1640 $cm^{-1}$; $^1H$ nmr (deuteriochloroform): δ 0.75-0.95 (t, 3H, J = 7 Hz), 1.10-1.32 (m, 5H), 1.35 (s, 3H), 1.67-1.95 (m, 4H), 2.30-2.60 (m, 2H), 3.70-3.90 (m, 2H), 4.10 (q, 2H, J = 7.1 Hz); $^{13}C$ nmr (deuteriochloroform): δ 13.9, 14.1, 17.3, 23.4, 23.9, 34.7, 36.0, 54.8, 60.3, 60.5, 174.0, 178.1.

*Anal.* Calcd. for $C_{12}H_{21}NO_2$: C, 68.21; H, 10.02; N, 6.63. Found: C, 67.96; H, 9.85; N, 6.70.

Ethyl 2-[2-(3,4-Dihydro-5*H*-pyrrolyl]-2-methyldecanoate (**5**) (n = 1, R = $n$-$C_8H_{17}$, R' = $CH_3$) (Method C).

This compound was obtained in a yield of 24%, bp 130°/0.5 Torr; ir (neat): ν 1720, 1630 $cm^{-1}$; $^1H$ nmr (deuteriochloroform): δ 0.92 (t, 3H, J = 7.1 Hz), 1.12-1.35 (m, 15H), 1.30 (s, 3H), 1.55-2.00 (m, 4H), 2.35-2.60 (m, 2H), 3.75-4.00 (m, 2H), 4.10 (q, 2H, J = 7 Hz); $^{13}C$ nmr (deuteriochloroform): δ 14.0, 14.2, 20.5, 22.6, 22.9, 26.1, 29.1, 30.0, 31.7, 31.9, 34.6, 36.0, 51.4, 60.5, 61.0, 174.5, 178.6.

*Anal.* Calcd. for $C_{17}H_{31}NO_2$: C, 72.55; H, 11.10; N, 4.98. Found: C, 72.38; H, 10.91; N, 5.07.

Ethyl 2-[2-(3,4-Dihydro-5*H*-pyrrolyl]-2-methyldodecanoate (**5**) (n = 1, R = $n$-$C_{10}H_{21}$, R' = $CH_3$) (Method C).

This compound was obtained in a yield of 12%, bp 93°/0.5 Torr; ir (neat): ν 1725, 1630 $cm^{-1}$; $^1H$ nmr (deuteriochloroform): δ 0.9 (t, 3H, J = 7 Hz), 1.12-1.35 (m, 19H), 1.40 (s, 3H), 1.73-2.04 (m, 4H), 2.35-2.57 (m, 2H), 3.75-3.95 (m, 2H), 4.15 (q, 2H, J = 7 Hz); $^{13}C$ nmr (deuteriochloroform): δ 14.1, 14.2, 20.5, 22.7, 22.9, 29.3, 29.4, 30.1, 31.8, 31.9, 34.6, 36.4, 51.1, 60.6, 60.8, 174.5, 178.7.

*Anal.* Calcd. for $C_{19}H_{35}NO_2$: C, 73.73; H, 11.40; N, 4.53. Found: C, 74.08; H, 11.23; N, 4.70.

Ethyl 2-[2-(3,4,5,6-Tetrahydro-6*H*-pyridyl]-2-methylpropanoate (**5**) (n = 2, R = R′ = $CH_3$) (Methods A or B).

This compound was obtained in a yield of 60% (A) or 58% (B), bp 90°/1 Torr; ir (neat): ν 1720, 1630 $cm^{-1}$; $^1H$ nmr (deuteriochloroform): δ 1.15 (t, 3H, J = 7.1 Hz), 1.25 (s, 6H), 1.50-1.60 (m, 4H), 2.00-2.15 (m, 2H), 3.50-3.60 (m, 2H), 4.10 (q, 2H, J = 7 Hz); $^{13}C$ nmr (deuteriochloroform): δ 14.2, 19.5, 21.6, 23.4, 25.8, 49.3, 60.9, 61.3, 171.0, 175.9.

*Anal.* Calcd. for $C_{11}H_{19}NO_2$: C, 66.97; H, 9.71; N, 7.10. Found: C, 67.14; H, 10.02; N, 6.89.

Ethyl 2-[2-(3,4,5,6-Tetrahydro-6*H*-pyridyl]-2-propylpentanoate (**5**) (n = 2, R = R′ = *n*-$C_3H_7$) (Method B).

This compound was obtained in a yield of 56%, bp 90°/0.1 Torr; ir (neat): ν 1725, 1655, $cm^{-1}$; $^1H$ nmr (deuteriochloroform): δ 0.8-1.00 (m, 6H), 1.20 (t, 3H, J = 7 Hz), 1.38-2.17 (m, 14H), 3.50-3.70 (m, 2H), 4.15 (q, 2H, J = 7 Hz); $^{13}C$ nmr (deuteriochloroform): δ 13.9, 14.3, 17.0, 19.2, 21.0, 26.2, 33.8, 48.9, 58.6, 59.9, 169.1, 174.5.

*Anal.* Calcd. for $C_{15}H_{27}NO_2$: C, 71.10; H, 10.74; N, 5.53. Found: C, 70.96; H, 10.52; N, 5.61.

Ethyl 2-[2-(3,4,5,6-Tetrahydro-6*H*-pyridyl]-2-octyldecanoate (**5**) (n = 2, R = R′ = *n*-$C_8H_{17}$) (Method B).

This compound was obtained in a yield of 61%, bp 160°/0.05 Torr; ir (neat): ν 1725, 1655 $cm^{-1}$; $^1H$ nmr (deuteriochloroform): δ 0.88 (t, 3H, J = 7 Hz), 1.00-1.35 (m, 32H), 1.50-2.00 (m, 6H), 2.05-2.15 (m, 2H), 3.50-3.75 (m, 2H), 4.05 (q, 2H, J = 7 Hz); $^{13}C$ nmr (deuteriochloroform): δ 14.1, 14.2, 19.5, 22.0, 22.7, 26.7, 29.4, 29.6, 30.1, 31.6, 32.0, 49.6, 58.9, 60.5, 170.0, 175.1.

*Anal.* Calcd. for $C_{25}H_{47}NO_2$: C, 76.28; H, 12.04; N, 3.56. Found: C, 75.93; H, 11.89; N, 3.61.

Ethyl 2-[2-(3,4,5,6-Tetrahydro-6*H*-pyridyl]-2-decyldodecanoate (**5**) (n = 2, R = R′ = *n*-$C_{10}H_{21}$) (Method B).

This compound was obtained in a yield of 33%, bp 120°/0.02 Torr; ir (neat): ν 1730, 1660 $cm^{-1}$; $^1H$ nmr (deuteriochloroform): δ 0.80 (t, 3H, J = 7 Hz), 0.88 (t, 3H, J = 7 Hz), 1.15-1.35 (m, 39H), 1.30-2.10 (m, 6H), 3.00-3.70 (m, 2H), 4.10 (q, 2H, J = 7 Hz); $^{13}C$ nmr (deuteriochloroform): δ 14.1, 14.3, 19.5, 22.0, 22.7, 23.8, 26.6, 29.4, 29.6, 29.7, 30.1, 31.5, 40.0, 49.4, 58.9, 60.4, 169.8, 175.1.

*Anal* Calcd. for $C_{29}H_{55}NO_2$: C, 77.44; H, 12.33; N, 3.11. Found: C, 77.20; H, 12.08; N, 3.09.

Ethyl 2-[2-(3,4,5,6-Tetrahydro-7*H*-azepinyl]-2-methylpropanoate (**5**) (n = 3, R = R = $CH_3$) (Methods A or B).

This compound was obtained in a yield of 65% (A) or 30% (B), bp 80°/0.05 Torr; ir (neat): ν 1730, 1660 $cm^{-1}$; $^1H$ nmr (deuteriochloroform): δ 1.26 (t, 3H, J = 7.1 Hz), 1.36 (s, 6H), 1.30-1.90 (m, 10H), 2.35-2.45 (m, 2H), 3.60-3.84 (m, 2H), 4.15 (q, 2H, J = 7.1 Hz); $^{13}C$ nmr (deuteriochloroform): δ 13.8, 22.9, 24.1, 25.9, 31.0, 31.1, 51.8, 52.5, 60.3, 175.5, 176.8.

*Anal.* Calcd. for $C_{14}H_{25}NO_2$: C, 70.25; H, 10.53; N, 5.85. Found: C, 69.98; H, 10.44; N, 5.82.

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