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A number of the title compounds have been prepared through a three step reaction sequence based on the cyclization of δ-acetal amides.

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As a part of our program to prepare optically active nitrogen heterocycles [1] we needed 3-*sec*-butyl-3,4-dihydro-2(1*H*)-pyridinone.

Since we have successfully synthesized 5-*sec*-butyl-3,4-dihydro-2(1*H*)-pyridinone by cyclization of methyl 4-formyl-5-methylheptanoate with ammonium acetate in acetic acid [2], we attempted an analogous procedure starting from ethyl 2-*sec*-butyl-2-(2-formylethyl)pentanoate [3]. Unexpectedly, the reaction of this compound with ammonium acetate in acetic acid failed and, although many permutations of conditions were explored (varying temperature, solvent, etc.) in no case could the desired lactam be obtained.

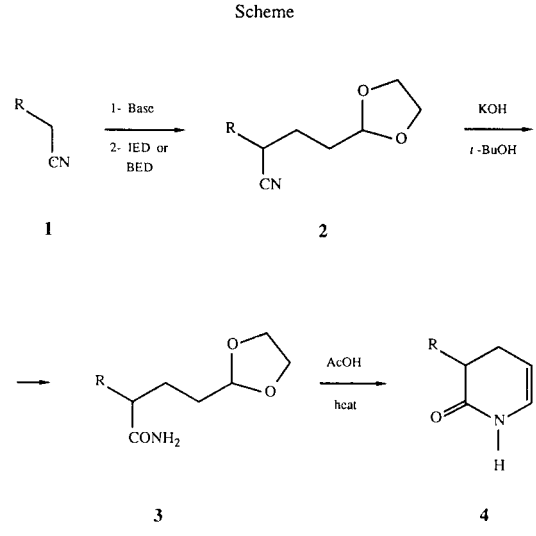
To overcome these difficulties a different approach was necessary. We now report a method for the anellation of nitriles to 3-substituted-3,4-dihydro-2(1*H*)-pyridinones [4].

As shown in the Scheme, the procedure entails a three step reaction sequence involving alkylation of the nitriles **1** with 2-(2-bromoethyl)- or 2-(2-iodoethyl)-1,3-dioxolane (BED or IED), followed by selective hydrolysis of δ-acetal nitriles **2** and finally by acid catalyzed cyclization of δ-acetal amides **3**. Aliphatic nitriles **1a,b,c** (Scheme) were metallated with lithium diisopropylamide in tetrahydrofuran at -78° and subsequently alkylated at -78° with IED, **1a,b**, or BED **1c**, followed immediately by addition of hexamethylphosphoric triamide (HMPT), to give compounds **2a,b,c** in good yields (75-77%) [5]. When BED was used in the alkylation of **1a** a 55% yield was obtained. Phenyl- and 2-(2-pyridyl)acetonitriles **1d,e** (Scheme) were alkylated with BED using a phase transfer technique [5]. Thus compounds **1d,e** were treated with a mixture of 50% sodium hydroxide, benzyltriethylammonium chloride and BED for 20 hours to give nitriles **2d,e** in satisfactory yields (49-72%).

Nitriles **2** were selectively converted into amides by refluxing in *t*-butyl alcohol containing powdered solid potassium hydroxide for 24 hours (73-93% yield). Only in the case of 2-(2-pyridyl)acetonitrile (**2e**) did we obtain unsatisfactory results (25% yield). It is interesting to note that the reaction time required for total conversion of nitriles to amides resulted in much longer periods of time than that reported for nitriles unsubstituted in the α-position [7].

The final step of this synthesis was carried out by refluxing compounds **3** in glacial acetic acid for 2 hours. 3-Substituted-3,4-dihydro-2(1*H*)-pyridinones were obtained in moderate yields (40-75%); only the amide **3e** failed to give the corresponding pyridinone.

Scheme



R = a: $(CH_3)_2CH$- b: C_2H_5-CH(-CH_3)- c: $CH_3(CH_2)_4CH_2$-

d : C_6H_5- e: 2-Pyridyl

EXPERIMENTAL

Boiling points are uncorrected. Melting points were determined on a Buchi 510 capillary apparatus and are uncorrected. The gc controls were effected on a Perkin Elmer 3920-B gas chromatograph, using a 2 m x 2 mm column packed with 5% SE-30 on Chromosorb W and operating at a programmed temperature (between 100° and 300°). The nmr spectra were obtained with a Varian T-60 spectrometer in tetrachloromethane solution unless otherwise stated using tetramethylsilane as an internal standard (δ = 0). The ir spectra were measured with a Perkin Elmer 1310 spectrophotometer. Elemental analyses were performed on a Perkin Elmer 240-B analyzer.

Materials.

All the nitriles and 2-(2-bromoethyl)-1,3-dioxolane (BED) were commercial products (Fluka AG) and were used without further

purification.

2-(2-Iodoethyl-1,3-dioxolane (IED) was prepared according to Larson *et al.* [8].

2-Alkyl-5,5-ethylenedioxypentanenitriles **2a,b,c.**

General Procedure.

To a solution of diisopropylamine (2.52 g, 25 mmoles) in THF (20 ml) a 1.6 *M* solution of *n*-butyllithium in *n*-hexane (15.7 ml) was added at -78°. After 15 minutes a solution of **1a,b,c** (25 mmoles) in THF (5 ml) was slowly added and stirring continued for 0.5 hour. A solution of IED for **1a,b**, or BED for **1c** (25 mmoles) in THF (5 ml) was slowly added, followed immediately by addition of HMPT (5 ml). After 1 hour at -78° the reaction mixture was allowed to rise to room temperature slowly and then treated with water and extracted with ether. The organic phase was dried over anhydrous sodium sulfate, evaporated, and fractionally distilled under reduced pressure to give pure **2a,b,c.**

2-*iso*-Propyl-5,5-ethylenedioxypentanenitrile (**2a**).

This compound was isolated in 75% yield, bp 100° (1 mm, Hg); ^{1}H nmr: 5.00-4.77 (m, 1H), 4.03-3.75 (m, 4H); ir (neat): 2228 cm^{-1}.

Anal. Calcd. for $C_{10}H_{17}NO_2$: C, 65.54; H, 9.35; N, 7.64. Found: C, 65.76; H, 9.50; N, 7.40.

2-*sec*-Butyl-5,5-ethylenedioxypentanenitrile (**2b**).

This compound was isolated in 77% yield, bp 113° (1 mm, Hg); ^{1}H nmr: 4.96-4.77 (m, 1H), 4.03-3.70 (m, 4H); ir (neat): 2230 cm^{-1}.

Anal. Calcd. for $C_{11}H_{19}NO_2$: C, 66.97; H, 9.71; N, 7.10. Found: C, 66.67; H, 9.85; N, 7.20.

2-*n*-Hexyl-5,5-ethylenedioxypentanenitrile (**2c**).

This compound was isolated in 75% yield, bp 120° (0.3 mm Hg); ^{1}H nmr: 4.92-4.71 (m, 1H), 4.02-3.70 (m, 4H); ir (neat): 2232 cm^{-1}.

Anal. Calcd. for $C_{13}H_{23}NO_2$: C, 69.29; H, 10.29; N, 6.21. Found: C, 69.32; H, 10.32; N, 6.30.

2-Aryl-5,5-ethylenedioxypentanenitriles **2d,e.**

General Procedure.

A mixture of **1d,e** (50 mmoles), BED (9.05 g, 50 mmoles), benzyltriethylammonium chloride (684 mg, 3 mmoles) and 50% sodium hydroxide solution (20 ml) was stirred vigorously for 20 hours at room temperature. The mixture was then diluted with water and extracted with ether. The ethereal solution was washed with water and dried over anhydrous sodium sulfate. After evaporation of the solvent the residue was purified by fractional distillation to give pure **2d,e.**

2-Phenyl-5,5-ethylenedioxypentanenitrile (**2d**).

This compound was isolated in 72% yield, bp 125° (0.5 mm, Hg); ^{1}H nmr: 7.35 (s, 5H), 4.88 (t, 1H), 4.07-3.70 (m, 5H); ir (neat): 2236 cm^{-1}.

Anal. Calcd. for $C_{13}H_{15}NO_2$: C, 71.85; H, 6.96; N, 6.45. Found: C, 71.55; H, 7.12; N, 6.75.

2-(2-Pyridyl)-5,5-ethylenedioxypentanenitrile (**2e**).

This compound was isolated in 49% yield, bp 180° (0.3 mm, Hg); ^{1}H nmr: 8.67-8.27 (m, 1H), 7.87-7.06 (m, 3H), 4.83 (t, 1H), 4.26-3.67 (m, 5H); ir (neat): 2242 cm^{-1}.

Anal. Calcd. for $C_{12}H_{14}N_2O_2$: C, 66.02; H, 6.47; N, 12.84. Found: C, 66.42; H, 6.26; N, 12.65.

2-Substituted-5,5-ethylenedioxypentaneamides **3.**

General Procedure.

To a stirred solution of **2** (25 mmoles) in 50 ml of *t*-butanol was added 5 g of finely powdered potassium hydroxide and the resulting mixture refluxed for 24 hours while stirring. The mixture was cooled and poured into 50 ml of an aqueous sodium chloride solution. The solution was extracted with methylene chloride and the organic phase dried over anhydrous sodium sulfate. Removal of the solvent *in vacuo* left a solid which after washing with petroleum ether gave pure amides **3.** Analytical samples were obtained by recrystallization from methylene chloride-diethyl ether.

2-*iso*-Propyl-5,5-ethylenedioxypentaneamide (**3a**).

This compound was isolated in 83% yield, mp 122-123°; ^{1}H nmr (deuteriochloroform): 6.03 (broad, 1H), 5.77 (broad, 1H), 4.97-4.73 (m, 1H), 4.07-3.73 (m, 4H), 2.03-1.40 (m, 6H), 0.92 (d, 6H); ir (nujol): 3340, 3150, 1640, 1620 cm^{-1}.

Anal. Calcd. for $C_{10}H_{19}NO_3$: C, 59.66; H, 9.52; N, 6.96. Found: C, 59.40; H, 9.35; N, 7.10.

2-*sec*-Butyl-5,5-ethylenedioxypentaneamide (**3b**).

This compound was isolated in 85% yield, mp 119-120°; ^{1}H nmr (deuteriochloroform): 6.23 (broad, 1H), 5.95 (broad, 1H), 4.97-4.70 (m, 1H), 4.01-3.76 (m, 4H); ir (nujol): 3340, 3155, 1645, 1620 cm^{-1}.

Anal. Calcd. for $C_{11}H_{21}NO_3$: C, 61.37; H, 9.83; N, 6.51. Found: C, 61.52; H, 9.70; N, 6.52.

2-*n*-Hexyl-5,5-ethylenedioxypentaneamide (**3c**).

This compound was isolated in 93% yield, mp 107-108°; ^{1}H nmr (deuteriochloroform): 6.07 (broad, 1H), 5.82 (broad, 1H), 4.93-4.73 (m, 1H), 4.10-3.77 (m, 4H); ir (nujol): 3340, 3150, 1630 cm^{-1}.

Anal. Calcd. for $C_{13}H_{25}NO_3$: C, 64.16; H, 10.36; N, 5.76. Found: C, 64.35; H, 10.22; N, 5.50.

2-Phenyl-5,5-ethylenedioxypentaneamide (**3d**).

This compound was isolated in 73% yield, mp 118-119°; ^{1}H nmr (deuteriochloroform): 7.23 (s, 5H), 5.54 (broad, 2H), 4.83 (t, 1H), 4.00-3.70 (m, 4H), 3.43 (t, 1H); ir (nujol): 3390, 3145, 1640 cm^{-1}.

Anal. Calcd for $C_{13}H_{17}NO_3$: C, 66.36; H, 7.28; N, 5.95. Found: C, 66.60; H, 7.50; N, 5.42.

2-(2-Pyridyl)-5,5-ethylenedioxypentaneamide (**3e**).

This compound was isolated in 25% yield, mp 152-153°; ^{1}H nmr (deuteriochloroform): 8.62-8.45 (m, 1H), 7.80-7.00 (m, 3H), 5.77 (broad, 2H), 4.85 (t, 1H), 4.03-3.43 (m, 5H); ir (nujol): 3270, 3110, 1665 cm^{-1}.

Anal. Calcd. for $C_{12}H_{16}N_2O_3$: C, 64.85; H, 7.26; N, 6.30. Found: C, 64.61; H, 7.30; N, 6.55.

3-Substituted-3,4-dihydro-2(1*H*)-pyridinones **4.**

General Procedure.

A solution of **3b** (30 mmoles) in acetic acid (150 ml) was refluxed for 2 hours. After cooling the solution was poured into water and extracted with ether. The ethereal solution was washed with a 10% sodium hydroxide solution and finally with water. The organic solution was dried over anhydrous sodium sulfate and

the solvent removed. Pure compounds **4** were isolated by usual methods, depending of its physical properties.

3-*iso*-Propyl-3,4-dihydro-2(1*H*)-pyridinone (**4a**).

This compound was isolated in 40% yield, bp 130° (0.2 mm, Hg); ^{1}H nmr: 8.03 (broad, 1H), 6.20-5.89 (m, 1H), 5.16-4.86 (m, 1H), 2.59-1.84 (m, 4H), 1.19-0.85 (m, 6H); ir (neat): 3230, 3095, 1670, 1650 cm^{-1}.

Anal. Calcd. for $C_8H_{13}NO$: C, 69.03; H, 9.41; N, 10.06. Found: C, 69.20; H, 9.56; N, 10.10.

2-*sec*-Butyl-3,4-dihydro-2(1*H*)-pyridinone (**4b**).

This compound was isolated in 42% yield, bp 140° (0.2 mm, Hg); ^{1}H nmr: 9.28 (broad, 1H), 6.23-5.90 (m, 1H), 5.17-4.81 (m, 1H); ir (neat): 3240, 3100, 1675 cm^{-1}.

Anal. Calcd. for $C_9H_{15}NO$: C, 70.55; H, 9.87; N, 9.14. Found: C, 70.10; H, 10.07; N, 9.34.

2-*n*-Hexyl-3,4-dihydro-2(1*H*)-pyridinone (**4c**).

This compound was isolated in 75% yield, mp 119-120°; ^{1}H nmr: 7.40-7.23 (m, 1H), 5.20-4.83 (m, 2H); ir (neat): 3340, 3200, 1610 cm^{-1}.

Anal. Calcd. for $C_{11}H_{19}NO$: C, 72.88; H, 10.56; N, 7.73. Found: C, 72.95; H, 10.70; N, 7.98.

2-Phenyl-3,4-dihydro-2(1*H*)-pyridinone (**4d**).

This compound was isolated in 71% yield, mp 112°; ^{1}H nmr: 8.65 (broad, 1H), 7.27 (s, 5H), 6.20-5.90 (m, 1H), 5.30-4.90 (m, 1H), 3.70 (t, 1H), 2.77-2.40 (m, 2H); ir (nujol): 3180, 3070, 1640 cm^{-1}.

Anal. Calcd. for $C_{11}H_{11}NO$: C, 76.28; H, 6.40; N, 8.09. Found: C, 76.58; H, 6.35; N, 8.29.

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[3] Ethyl 2-*sec*-butyl-2-(2-formylethyl)pentanoate has been prepared in 52% overall yield by metallation (LDA, THF, -78°) of ethyl 3-methylpentanoate, followed by alkylation (-78°) with 2-(2-iodoethyl)-1,3-dioxolane and finally by acid catalyzed deprotection of formyl function. This compound had bp 95° (0.4 mm, Hg); ^{1}H nmr (carbon tetrachloride): 9.70 (1H, s), 4.20 (2H, q), 1.22 (3H, t).

Anal. Calcd. for $C_{11}H_{20}O_3$: C, 65.96; H, 10.07. Found: C, 66.12; H, 10.23.

[4] For a review on 3,4-dihydro-2(1*H*)-pyridinones see: J. Jones in "Comprehensive Heterocyclic Chemistry", Vol **2**, Part 2A, A. J. Boulton and A. McKillop, eds, Pergamon Press, New York, 1984, pp 404, 436, 442 and 461.

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