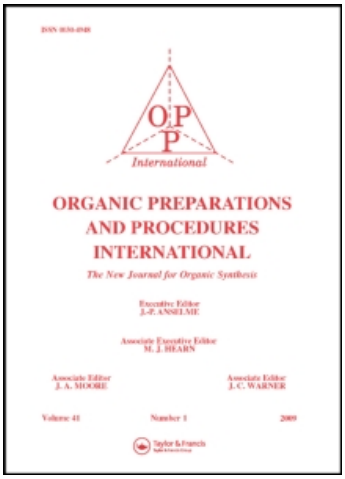

Organic Preparations and Procedures International
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t902189982

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E. R. Lavagnino[a]; C. W. Ryan[a]
[a] The Lilly Research Laboratories, Eli Lilly and Company, Indianapolis, Indiana

To cite this Article Lavagnino, E. R. and Ryan, C. W.(1983) 'THE REACTION OF *trans*-3-HEXENEDIOIC ACID WITH ETHYLENEDIAMINES. A SIMPLE ROUTE TO THE TETRAHYDRO-1H-PYRROLO[1,2-d][1,4]DIAZEPINE RING SYSTEM', Organic Preparations and Procedures International, 15: 4, 251 — 260
To link to this Article: DOI: 10.1080/00304948309356650
URL: http://dx.doi.org/10.1080/00304948309356650

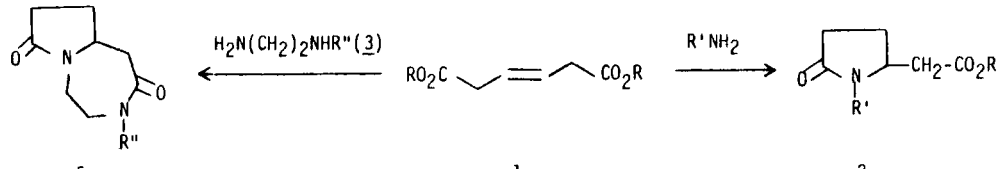
ORGANIC PREPARATIONS AND PROCEDURES INT. 15(4), 251-260 (1983)

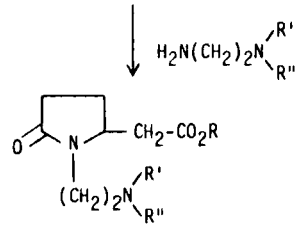
THE REACTION OF trans-3-HEXENEDIOIC ACID WITH ETHYLENEDIAMINES. A SIMPLE ROUTE TO THE TETRAHYDRO-1H-PYRROLO[1,2-d][1,4]DIAZEPINE RING SYSTEM

E. R. Lavagnino* and C. W. Ryan

The Lilly Research Laboratories, Eli Lilly and Company
Indianapolis, Indiana 46285

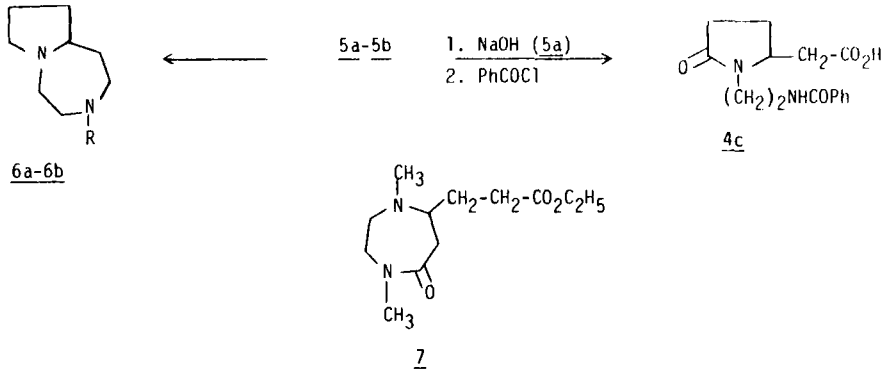
The reaction of trans-3-hexenedioic acid (1a) with primary amines to form 5-oxo-2-pyrrolidine acetic acids (2) was initially discovered by Evans et al.[1] The utility of this route to prepare pyrrolidine acetic acids and esters has been amply demonstrated in subsequent studies.[2-4]





We have found that replacing the primary amine reactant with a series of ethylenediamines (3a-3d) has resulted in the formation of tetrahydro-1H-pyrrolo[1,2-d][1,4]diazepine-2,7(3H,8H)diones (5a-5d) which can readily

be reduced to octahydro-1H-pyrrolo[1,2-d][1,4]-diazepines (6). Since the starting materials (1a-1c and 3a-3d) are readily available and the yields



6a-6b

4c

7

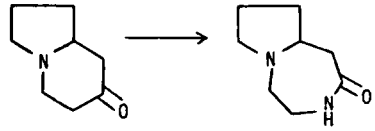
are respectable, this synthetic route becomes an easy, efficient method for the preparation of 6. Thus heating an ethanol solution of 1a and 3a in an autoclave at 200° gives, after workup, the dilactam 5a in 37% yield. Substitution of the diethyl ester (1b) for the diacid (1a) increases the yield of 5a to 68%. A slightly lower yield (61%) of 5a is achieved by heating a diglyme solution of the dimethyl ester (1c) and 3a at reflux for 3 hrs.

The evidence for the structural assignment of 5a is two-fold. First, spectral data (mass and ^{13}C NMR spectra) are consistent with the proposed structure. Secondly, three chemical conversions of 5a also validate the structural assignment. Treatment of 5a with base cleaves the seven membered ring lactam to the amino acid 4c (isolated as the benzamide derivative). Octahydro-1H-pyrrolo[1,2-d][1,4]diazepine (6a) is formed from lithium aluminum hydride reduction of 5a. And finally 5a was converted to a urea derivative (5e) by treatment with phenyl isocyanate.

Although the monoalkyl substituted ethylenediamines (3b-3d) yield as products the 3 substituted dilactams (5b-5d), N-phenylethylenediamine does not give a similar product. Instead, only the open-ring, amino

ester (4a) could be isolated from the reaction mixture. In an attempt to cyclize 4a it was heated at 275° in ethanol solution in an autoclave for 24 hours but only starting material was recovered. It had been presumed that amino esters 4 were intermediates in the cyclization reaction. No attempts however were made to modify conditions in the reaction (1+3→5) so as to isolate them. Consequently, there is no certain evidence for the path of the reaction. In the case where the formation of the seven-membered ring lactam is blocked by disubstitution of one amino group of the ethylenediamine (N,N,-dimethylethylenediamine), the amino ester 4b is formed in 52% yield as the only isolated product. In one experiment in which both amino groups of the ethylenediamine were monosubstituted (N,N' dimethylethylenediamine), a low yield of the diazepine 7 was obtained.

Compounds of types 5 and 6 have apparently not been described; however, a closely related compound, hexahydro-1H-pyrrolo[1,2-d][1,4]-diazepine-2(3H)-one (9) has been synthesized[5] via the Schmidt reaction on the ketone 8.



8 9

EXPERIMENTAL

Melting points are uncorrected. NMR spectra were determined at 60 MHz on a Varian Associates T-60 Spectrometer. Mass spectra were determined on a CEC 21-110 spectrometer at an ionizing voltage of 70 eV. Infrared spectra were obtained using a Perkin-Elmer Model 457 diffraction grating spectrophotometer and a Nicolet MX-1. ^{13}C NMR spectra were determined on Varian FT-80A and JEOL PG-100 spectrometers. Preparative HPLC's were performed on a Waters Associates Prep LC system 500. trans-3-Hexenedioic acid (1a) and the ethylenediamines were all commercially available.

trans-3-Hexenedioic acid diethyl ester (1b) was prepared in 85% yield by the method of Wu et al.[2] Pure 1b is a clear liquid with bp. 105-107/7 mm., lit.[2] 144-148°/23 mm. A sample of 1b applied to a silica gel precoated TLC plate and developed with EtOAc indicated one spot material when visualized by exposure to iodine vapor.

NMR ($CDCl_3$): δ 1.3 (t, 6, CH_3), 3.1 (m, 4, $-CH_2C=O$), 4.2 (q, 4, $-OCH_2$), 5.7 (m, 2, $-CH=CH-$). IR ($CHCl_3$): 3010, 2997, 1725, 1370 cm^{-1}; MS m/e 200 (M^+).

trans-3-Hexenedioic acid dimethyl ester (1c) was prepared in 82% yield as above, bp. 93-94°/6-7 mm. A sample of 1c applied to a silica gel precoated TLC plate and developed with EtOAc indicated one spot material when visualized by exposure to iodine vapor.

Anal. Calcd. for $C_8H_{12}O_4$: C, 55.81; H, 7.03 Found: C, 56.09; H, 6.84

NMR ($CDCl_3$): δ 3.1 (m, 4, $-CH_2C=O$), 3.7 (s, 6, $-OCH_3$), 5.7 (m, 2, $-CH=CH-$). IR ($CHCl_3$): 3010, 2978, 1740, 1430 cm^{-1}; MS m/e 172 (M^+).

Tetrahydro-1H-pyrrolo[1,2-d][1,4]diazepine-2,7(3H,8H)-dione (5a).

Method a.- A mixture of 44.0 g (0.3 mol) of trans-3-hexenedioic acid (1a) and 18 g (0.3 mol) of ethylenediamine (3a) was placed in an autoclave with 250 ml of EtOH. After heating at 200° for 6 hrs, the contents were removed at room temperature and the solvent was concentrated at reduced pressure leaving a semi-solid residue. Trituration in cold EtOH provided crystals that were collected and recrystallized from EtOH giving 18.6 g (37%) of white crystals, mp. 196-198°. A sample of 5a applied to a silica gel precoated TLC plate and developed with MeOH indicated one spot material when visualized by exposure to iodine vapor.

Anal. Calcd. for $C_8H_{12}N_2O_2$: C, 57.13; H, 7.19; N, 16.66

Found: C, 56.93; H, 6.95; N, 16.62

^{13}C NMR, (D_2O): δ 178.3 (C=O), 178.3 (C=O), 67.4 (CH), 56.0, 43.9, 41.8, 30.5, 25.7 (CH_2's). IR ($CHCl_3$): 3420, 3010, 1673, 1467, 1459, 1440, 1423, 1356, 1346, 1293 cm^{-1}; MS m/e 168 (M^+).

Method b.- A mixture of 40 g (0.2 mol) of trans-3-hexenedioic acid diethyl ester (1b), 14 g (0.23 mol) of 3a and 150 ml of EtOH was heated in an autoclave at 200° for 6 hrs. After cooling the contents were removed and the solvent was concentrated to provide 24 g of a white solid after trituration in cold EtOH. Recrystallization from acetonitrile gave 22.8 g (68%) of 5a identical with the material obtained by method a above.

Method c.- A mixture of 34.2 g (0.2 mol) of trans-3-hexenedioic acid dimethyl ester (1c) and 12 g (0.2 mol) of 3a was refluxed with stirring in 100 ml of diglyme under an atmosphere of nitrogen. After 1 h white crystals began to appear in the previously homogeneous solution. After 3 hrs the reaction was stopped, and the reaction mixture was refrigerated overnight. The crystals were then collected and washed with cold diglyme to yield after drying 20.5 g (61%) of 5a identical with the material prepared by methods a and b above.

Tetrahydro-3-methyl-1H-pyrrolo[1,2-d][1,4]diazepine-2,7(3H,8H)-dione (5b) was prepared in 65% yield from 1b and 3b using method b (above). The pure material had mp. 166-168° after recrystallization from EtOAc.

Anal. Calcd. for $C_9H_{14}N_2O_2$: C, 59.32; H, 7.74; N, 15.37

Found: C, 59.31; H, 7.50, N, 15.09

IR ($CHCl_3$): 3005, 1680, 1640, 1485, 1435, 1420, 1400, 1355, 1345, 1295 cm^{-1}; MS m/e 182 (M^+).

Tetrahydro-3-ethyl-1H-pyrrolo[1,2-d][1,4]diazepine-2,7(3H,8H)-dione (5c) was prepared in 60% yield from 1b and 3c using method b (above). The pure material had mp. 108-110° after recrystallization from EtOAc-hexane.

Anal. Calcd. for $C_{10}H_{16}N_2O_2$: C, 61.22; H, 8.22; N, 14.29
Found: C, 61.49; H, 7.95; N, 13.81

IR ($CHCl_3$): 3005, 1680, 1640, 1480, 1435, 1420, 1360, 1295 cm^{-1}; MS m/e 196 (M^+).

Tetrahydro-3-(phenylmethyl)-1H-pyrrolo[1,2-d][1,4]diazepine-2,7(3H,8H)-dione (5d) was prepared in 70% yield from 1b and 3d using method b (above). The pure material had mp. 150-152° after recrystallization from EtOAc.

Anal. Calcd. for $C_{15}H_{18}N_2O_2$: C, 69.74; H, 7.02; N, 10.84
Found: C, 69.80; H, 6.86; N, 10.64

IR ($CHCl_3$): 3015, 1680, 1640, 1435, 1425, 1365, 1300, 1250 cm^{-1}; MS m/e 258 (M^+).

4,5,9,9a-Tetrahydro-2(3H),7(8H)-dioxo-1H-pyrrolo[1,2-d][1,4]diazepine-3-carboxanilide (5e).- Using the procedure of Wiley,[6] 1.68 g (0.01 mol) of 5a and 1.19 g (0.01 mol) of phenyl isocyanate were refluxed overnight in 100 ml of toluene. The reaction mixture was then concentrated to a solid and recrystallized from EtOH providing a 76% yield of 5e, mp. 185-187°.

Anal. Calcd. for $C_{15}H_{17}N_3O_3$: C, 62.70; H, 5.96; N, 14.63
Found: C, 62.49, H, 5.76; N, 14.51

IR ($CHCl_3$): 3000, 1710, 1685, 1600, 1550, 1450, 1425, 1400, 1345, 1315 cm^{-1}; MS m/e 287 (M^+).

5-Oxo-1-[2-(phenylamino)ethyl]-2-pyrrolidineacetic acid, ethyl ester (4a).- By using method b the amino ester compound 4a was obtained in 57% yield, mp. 101-103° (from EtOH) from the diester 1b and N-phenylethyl-enediamine.

Anal. Calcd. for $C_{16}H_{22}N_2O_3$: C, 66.18, H, 7.63; N, 9.65
Found: C, 65.75; H, 7.32; N, 9.70

IR ($CHCl_3$): 3380, 3000, 1725, 1675, 1600, 1505, 1415, 1375, 1315, 1250 cm^{-1}; MS m/e 290 (M^+).

5-Oxo-1-[2-(dimethylamino)ethyl]-2-pyrrolidineacetic acid methyl ester (4b).- A solution of 34.4 g (0.2 mol) of 1c and 17.6 g of N,N-dimethylethylenediamine was refluxed in 150 ml of diglyme under a nitrogen atmosphere for 24 hrs. The solvent was then removed to provide a thick dark oil which was subjected to vacuum distillation. The fraction with bp. 160-170°/7 mm representing a 52% yield was mainly one spot material when applied to a silica gel precoated TLC plate, developed with MeOH and visualized by exposure to iodine vapor, but contained some minor impurities. Since the mass spectrum indicated m/e (228^+) this material was not purified further but was used to prepare the maleate and hydrochloride salts as described next.

The oil (8 g) was dissolved in 25 ml of EtOH and added to a solution of 4 g of maleic acid in 25 ml of EtOH. After standing for 1 h at rt., the solution was diluted with ether to the cloud point; after standing for 3 hrs, the crystals that had separated were collected and recrystallized twice from EtOH providing 7.5 g of white crystals of the maleate salt, mp. 121-123°. MS m/e 228 (M^+).

Anal. Calcd. for $C_{15}H_{24}N_2O_7$: C, 52.32; H, 7.03; N, 8.13
Found: C, 52.19; H, 6.96; N, 8.23

The hydrochloride salt was prepared by dissolving a small amount of the oil in EtOH and adding the solution to an ether solution that had been saturated with anhydrous HCl. The gummy solid that formed was triturated in EtOH and ether until crystalline and recrystallized from EtOH-ether to give white crystals, mp. 157-159°.

Anal. Calcd. for $C_{11}H_{21}ClN_2O_3$: C, 49.90; H, 8.00; N, 10.58
Found: C, 49.70; H, 7.87; N, 10.84

5-Oxo-1-[2-(benzoylamino)ethyl]-2-pyrrolidineacetic acid (4c).- A solution of 5a (2.0 g; 0.012 mol) and 4.0 g of NaOH was refluxed in 100 ml of H_2O for 3 hrs. The reaction mixture was then cooled in an ice bath and 75 ml of acetone was added. 4.0 g of benzoylchloride in 25 ml of acetone was then added dropwise with stirring over a 0.5 h period. The reaction mixture was then allowed to warm to room temperature over-night. The acetone was then removed in vacuo and the solution was acidified with HCl. The solid precipitate that formed (benzoic acid) was removed by extraction into ether. The remaining aqueous acidic solution was concentrated to one-half its volume and the solid that separated was collected and recrystallized from EtOH providing pure 4c in 44% yield, mp. 190-192°.

Anal. Calcd. for $C_{15}H_{18}N_2O_4$: C, 62.05; H, 6.25; N, 9.65
Found: C, 61.88; H, 6.34; N, 9.64

IR (KBr): 3300, 3080, 2980, 2955, 1721, 1668, 1628, 1603, 1576, 1560, 1449, 1303, 1183, 850 cm^{-1}; MS m/e 290 (M^+).

Octahydro-1H-pyrrolo[1,2-d][1,4]diazepine (6a).- To a slurry of 8 g (0.22 mol) of lithium aluminum hydride in 300 ml of THF was added 12 g (71 mmol) of 5a. The mixture was stirred and cooled in an ice bath until the exotherm subsided, then heated under reflux for 16 hrs. The mixture was then cooled in an ice bath while 8 ml of H_2O, 8 ml of 4N NaOH and 25 ml of H_2O were successively added. The solid phase was removed by filtration and washed with THF. The filtrate and washings were dried over K_2CO_3 and evaporated to give 9.2 g of crude 6a. Distillation gave 7.8 g (78%) of purified material, bp. 90-92°/17 mm.

Anal. Calcd. for $C_8H_{16}N_2$: C, 68.52; H, 11.50; N, 19.98
Found: C, 68.48; H, 11.54; N, 19.79

^{13}C NMR ($CHCl_3$): δ64.1 (CH), 57.7, 57.5, 48.7, 46.8, 37.2, 33.2, 23.0 (CH_2's); MS m/e 140 (M^+).

The dihydrochloride was crystallized from a 2-propanol solution of 6a to which excess anhydrous HCl in 2-propanol had been added, mp. 173-175°.

Anal. Calcd. for $C_8H_{18}Cl_2N_2$: C, 45.08; H, 8.51; Cl, 33.27; N, 13.14
Found: C, 44.80; H, 8.34; Cl, 33.44; N, 13.32

The N-p-toluenesulfonyl derivative (mp. 95-97°) was prepared using p-toluene sulfonyl chloride in CH_2Cl_2.

Anal. Calcd. for $C_{15}N_{22}N_2O_2S$: C, 61.19; H, 7.53; N, 9.52; O, 10.87
Found: C, 61.28; H, 7.42; N, 9.27; O, 11.09

Octahydro-3-methyl-1H-pyrrolo[1,2-d][1,4]diazepine (6b).- Treatment of 10 g (0.055 mol) of 5b with LAH in a manner similar to the preparation of 6a from 5a (above) produced 8.3 g of crude product after work up. Distillation yielded 6.8 g (80%) of one component material (by G.C.), bp. 95-96°/22 mm. MS m/e 154 (M^+). IR ($CHCl_3$): no carbonyl. This material (2 g) was dissolved in 10 ml of 2-propanol and a solution of anhydrous HCl in 2-propanol added. The crystals that separated after cooling the mixture were collected, washed with cold 2-propanol and dried to provide 2.5 g (85%) of the dihydrochloride of 6b, mp. 219-221°.

Anal. Calcd. for $C_9H_{20}Cl_2N_2$: C, 47.58; H, 8.87; N, 12.33; Cl, 31.21
Found: C, 47.37; H, 8.62; N, 12.44; Cl, 31.47

Hexahydro-1,4-dimethyl-7-oxo-1H-1,4-diazepine-5-propanoic acid, ethyl ester, hydrochloride (7).- A solution of 36.6 g (0.183 mol) of 1b and 16.1 g (0.183 mol) of N,N'-dimethylethylenediamine was refluxed in 100 ml of diglyme under an atmosphere of nitrogen for 24 hrs. The reaction mixture was concentrated, poured into water, acidified with dilute HCl and extracted with ether to remove unreacted 1b. The solution was then neutralized with $NaHCO_3$ and extracted with ethyl acetate.

Concentration of the ethyl acetate extract provided an oil (9.9 g) that was mainly one spot material when applied to a silica gel precoated TLC plate, developed with a 3:1 CH_2Cl_2-EtOH mixture and visualized by exposure to iodine vapor, but contained some minor impurities. Purification by preparative HPLC provided 4.7 g of one spot material (exact mass determination Calcd. for $C_{12}H_{22}N_2O_3$: Found: 242.16326; Calcd. 242.16303). The hydrochloride salt was prepared and recrystallized from 2-propanol, mp. 143-145°.

Anal. Calcd. for $C_{12}H_{23}ClN_2O_3$: C, 51.70; H, 8.32; N, 10.05

Found: C, 52.00; H, 8.44; N, 10.25

NMR ($CDCl_3$): δ 1.3 (t, 3, CH_3), 2.9 (s, 3, CH_3), 3.1 (s, 3, CH_3), 4.2 (q, 2, $-O\underline{CH_3}$), 12.8 (bs, 1, H) exchanges with D_2O. The remaining signals were overlapping multiplets in the range δ 1.5-5.0. IR ($CHCl_3$): 3420, 2980, 2300, 1735, 1665, 1480, 1460, 1400, 1380, 1360, 1300 cm^{-1}.

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(Received January 13, 1983; in revised form June 6, 1983)