A New Entry to Pyrazolo[4,3-*e*][1,4]diazepines. Facile Synthesis of Pyrazolo [4,3-*e*][1,4]diazepin-5,8-diones, 5,6,8-Triones and Pyrazolo[4,3-*e*]pyrrolo-[1,2-*a*][1,4]diazepin-5,10-diones

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A facile approach to pyrazolo[4,3-*e*][1,4]diazepin-5,8-diones and pyrazolo[4,3-*e*]pyrrolo[1,2-*a*][1,4]-diazepin-5,10-diones is reported. Strategy involved the utility of α-amino acid as a three-atom segment in the construction of diazepine skeleton on the preformed pyrazole ring.

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Introduction.

Immense pharmacological importance of [1,4]benzodiazepines [1] led to a great deal of work on various facets of heteroannelated[1,4]diazepines. Thus, [1,4]diazepines fused to thiophenes [2], imidazoles [3], pyrroles [4], isoxazoles [5] and pyrazoles [6-7] were synthesized and investigated for their pharmacological activity.

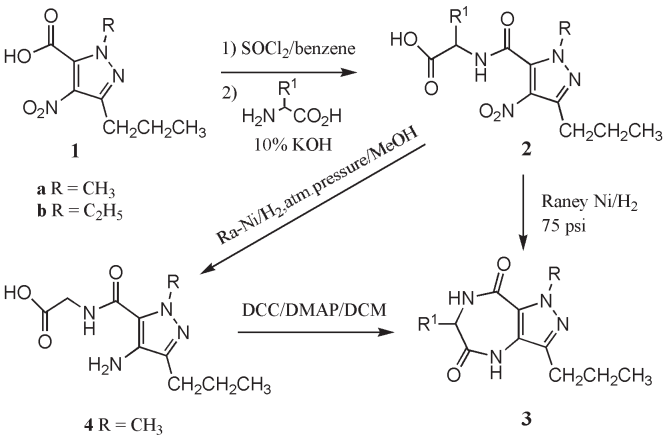
Our current interest in fused pyrazoles coupled with above findings prompted us to plan the synthesis of pyrazolo[4,3-*e*][1,4]diazepine derivatives. Earlier, Dewald and co-workers [6] reported the synthesis of 1,3/2,3-dialkyl-4,6-dihydro-8-aryl pyrazolo[4,3-*e*][1,4]diazepine-5-ones by making use of 1,3/2,3-dialkyl-4-aminopyrazolyl aryl ketones as intermediates. In the present paper, we describe the synthesis of various new fused pyrazolodiazepine derivatives through a short synthetic sequence. Utility of α-amino acids as a three atom segment in the construction of diazepine skeleton on the preformed pyrazole ring served as a facile route to pyrazolo[4,3-*e*][1,4]diazepines. 1-Alkyl-4-nitro-3-*n*-propyl pyrazolyl-5-carboxylic acid [8] **1a/1b** was chosen as the precursor.

Results and Discussion.

Reaction of **1a** with thionyl chloride and subsequent condensation of the resulting acid chloride with glycine in 10% KOH solution afforded 1-methyl-3-*n*-propyl-1*H*-pyrazolyl-5-carboxamido)acetic acid **2a**. Treatment of **2a** with hydrogen in the presence of Raney nickel at 75 psi pressure directly furnished 1-methyl-3-*n*-propyl-1,4,5,6,7,8-hexahydropyrazolo[4,3-*e*][1,4]diazepin-5,8-dione **3a** in 73% yield. The structural assignment of **3a** was based on its ir, mass, ^{1}H and ^{13}C nmr spectral data.

In the mass spectrum of **3a** the highest peak at m/e 222 corresponds to the molecular ion. Presence of two distinct amide functions in the compound is deduced from the ir spectrum [KBr, 3178, 3070 cm^{-1} (two amide NH); 1689, 1669 cm^{-1} (amide carbonyls)]. ^{1}H nmr spectrum (DMSO-d_6) displayed two amide proton signals at δ 10.1 (br s, 1H) and δ 8.3 (t, 1H) while doublet at δ 3.6 integrating for two protons is assignable to glycine CH_2 group. Other signals in the ^{1}H nmr spectrum are due to *N*-methyl (δ 4.0, s, 3H) and *n*-propyl [δ 1.0 (t, 3H, CH_3), 1.6 (m, 2H, CH_2), 2.6 (t, 2H, CH_2)]. ^{13}C nmr spectrum of **3a** showed a total of ten signals. They include signals in the downfield region due to two carbonyl carbons (δ 168.6 and 161.7) and three carbons of pyrazole nucleus (δ 148.6, 125.1 and 121.6). In the upfield region, the five signals at δ 13.3, 21.5, 26.4, 38.2 and 45.3 are due to *n*-propyl, *N*-methyl and *N*-methylene carbons. Thus, in the Raney nickel reduction of nitropyrazolylglycine derivative **2a** at 75 psi pressure, initially formed aminopyrazolylglycine intermediate **4** is undergoing concomitant dehydrocylisation under the reaction conditions to provide the pyrazolodiazepine dione **3a** in one

Scheme 1



Compds. **2** and **3**	**a**	**b**	**c**	**d**	**e**
R	CH_3	CH_3	CH_3	CH_3	C_2H_5
R^1	H	CH_3	$CH(CH_3)_2$	H_2C–Ph	H

step. To verify this, compound **2a** was subjected to Raney Ni reduction under mild conditions (at atmospheric pressure) and open chain intermediate **4** was isolated as the product. Compound **4** smoothly cyclised into **3a** in the presence of 1,3-dicyclohexylcarbodiimide.

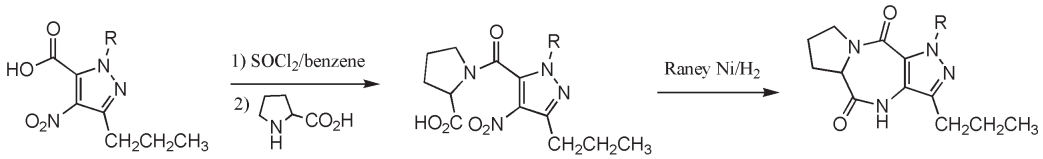
Three other α-aminoacids, L-alanine, L-valine and L-phenylalanine furnished the corresponding pyrazolodiazepines **3b-d** in good yields (Scheme-1). 1-Ethyl pyrazole derivative **1b** provided the corresponding pyrazolodiazepine derivative **3e** by participating in reaction with glycine through a similar synthetic sequence. A similar two step synthetic operation starting from **1a**/**1b** and L-proline yielded novel fused tricyclic compounds, pyrazolo[4,3-*e*]-pyrrolo[1,2-*a*]diazepin-5,10-diones **3f-g** (Scheme-2).

Condensation of 1-alkyl-4-amino-3-*n*-propylpyrazole-5-carboxamide **5a**/**5b** with oxalyl chloride in dichloromethane in the presence of pyridine directly yielded 1-alkyl-3-*n*-propyl-1,4,5,6,7,8-hexahydropyrazolo[4,3-*e*]-[1,4]diazepin-5,6,8-triones **6a**/**6b** (Scheme-3). All the pyrazolodiazepines were characterized based on their ir, mass and ^{1}H nmr spectral data (Table-1).

Conclusion.

Thus, we have provided a facile new entry to pyrazolo[4,3-*e*][1,4]diazepines. Novel fused tricyclic compounds, pyrazolo[4,3-*e*]pyrrolo[1,2-*a*]diazepines were obtained by this synthetic procedure.

Scheme 2



1a R = CH_3
2b R = C_2H_5

2f R = CH_3
2g R = C_2H_5

3f R = CH_3
3g R = C_2H_5

Table 1

Physical and Spectral Data of 2-(1-Alkyl-4-nitro-3-*n*-propyl-1*H*-pyrazolyl-5-carboxamido)substituted Carboxylic Acids **2**, Pyrazolodiazepindiones **3** and Pyrazolodiazepintriones **6**

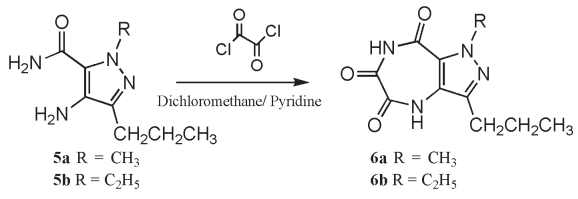
Compd. No.	m.p. (°C)	Yield (%)	ir	^{1}H nmr	MS (m/z) (M^+)
2a	174	85	3246 1725 1654	1.0 (t, 3H, CH_3), 1.7 (m, 2H, CH_2), 2.85 (t, 2H, CH_2), 3.9 (s, 3H, N-CH_3), 4.1 (d, 2H, N-CH_2), 8.9 (br s, 1H, NH)	270
2b	139	83	3306 1709 1650	1.0 (t, 3H, CH_3), 1.6 (m, 2H, CH_2), 2.4 (d, 3H, CH_3), 2.7 (t, 2H, CH_2), 4.0 (s, 3H, N-CH_3), 4.4 (m, 1H, CH), 8.5 (br s, 1H, NH)	284
2c	78	76	3271 1725 1646	1.0 (m, 9H, 3 x CH_3), 1.8 (m, 3H, CH and CH_2), 2.85 (t, 2H, CH_2), 3.95 (s, 3H, N-CH_3), 4.7 (m, 1H, CH), 8.4 (d, 1H, NH)	312
2d	183	71	3268 1703 1654	1.0 (t, 3H, CH_3), 1.7 (m, 2H, CH_2), 2.8 (t, 2H, CH_2), 3.2 (m, 2H, Ar-CH_2), 4.0 (s, 3H, N-CH_3), 4.2 (m, 1H, CH), 7.2 (m, 5H, Ar-H), 8.0 (br d, 1H, NH)	360
2e	160	81	3247 1721 1662	0.95 (t, 3H, CH_3), 1.35 (t, 3H, N-C-CH_3), 1.6 (m, 2H, CH_2), 2.4 (t, 2H, CH_2), 4.1 (d, 2H, N-CH_2), 4.3 (q, 2H, N-CH_2), 8.6 (br s, 1H, NH)	284
2f	55	71	1734 1654	1.0 (t, 3H, CH_3), 1.8 (m, 2H, CH_2), 2.2-2.6 (m, 4H, CH_2 and two pyrrolidine protons), 2.9 (m, 2H, CH_2), 3.4 (br s, 2H), 3.9 (s, 3H, N-CH_3), 4.8 (t, 1H, C_5-H), 8.9 (br s, 1H, OH)	310
2g	48	76	1725 1651	1.0 (t, 3H, CH_3), 1.45 (t, 3H, N-C-CH_3), 1.7 (m, 2H, CH_2), 2.1 (m, 2H, CH_2), 2.2 (m, 1H), 2.4 (m, 3H, CH and CH_2), 2.8 (m, 2H), 4.2 (m, 2H, CH_2), 4.8 (m, 1H, NH), 9.8 (br s, 1H, OH)	324

Table 1 (continued)

Compd. No.	m.p. (°C)	Yield (%)	ir	^{1}H nmr	MS (m/z) (M^+)	CHNAnalysis
3a	199 [a]	81	3178 3070 1689 1669	1.0 (t, 3H, CH_3), 1.6 (m, 2H, CH_2), 2.6 (t, 2H, CH_2), 4.0 (s, 3H, N-CH_3), 3.6 (d, 2H, N-CH_2), 8.3 (br s, 1H, NH), 10.1 (br s, 1H, NH)	222	Calcd: C, 54.04; H, 6.35; N, 25.21. Found: C, 54. 19; H, 6.33; N, 25.29.
3b	215 [a]	78	3326 3155 1699 1669	1.0 (t, 3H, CH_3), 1.7 (m, 2H, CH_2), 2.4 (d, 3H, CH_3), 2.7 (t, 2H, CH_2), 4.0 (s, 3H, NCH_3), 4.6 (m, 1H, CH), 7.4 (br s, 1H, NH), 7.9 (br s, 1H, NH)	236	Calcd: C, 54.92; H, 6.83; N, 23.71. Found: C, 55.11; H, 6.82; N, 23.78.
3c	159 [a]	75	3271 3108 1703 1696	1.1 (m, 9H, 3 x CH_3), 1.7 (m, 2H, CH_2), 2.3 (m, 1H, CH), 2.9 (t, 2H, CH_2), 4.0 (s, 3H, N-CH_3), 4.6 (d, 1H, CH), 8.0 (d, 1H, NH), 8.3 (br s, 1H, NH)	264	Calcd: C, 59.07; H, 7.63; N, 21.20. Found: C, 59.24; H, 7.61; N, 21.27.
3d	89 [a]	69	3281 3095 1697 1649	0.9 (t, 3H, CH_3), 1.7 (m, 2H, CH_2), 2.6 (t, 2H, CH_2), 3.1 (d, 2H, Ar-CH_2), 3.6 (m, 1H, CH), 4.0 (s, 3H, N-CH_3), 7.3 (m, 5H, Ar-H), 8.6 (br s, 1H, NH), 10.2 (br s, 1H, NH)	312	Calcd: C, 65.37; H, 6.45; N, 17.94. Found: C, 65.53; H, 6.44; N, 17.99.
3e	163 [a]	77	3324 3153 1694 1666	1.0 (t, 3H, CH_3), 1.4 (t, 3H, N-C-CH_3), 1.7 (m, 2H, CH_2), 2.6 (t, 2H, CH_2), 3.8 (d, 2H, N-CH_2), 4.4 (q, 2H, N-CH_2), 7.5 (br, t, 1H, NH), 9.3 (br s, 1H, NH)	236	Calcd: C, 55.92; H, 6.83; N, 23.71. Found: C, 56.09; H, 6.83; N, 23.77.
3f	183 [a]	80	3160 1684 1653	1.0 (t, 3H, CH_3), 1.6 (m, 2H, CH_2), 2.6 (m, 2H, CH_2), [2.0 (br s, 3H), 2.8 (m, 1H), 3.6 (m, 2H), 4.1 (m, 1H, due to pyrrolidine protons)], 4.0 (s, 3H, N-CH_3), 9.4 (br s, 1H, NH)	262	Calcd: C, 59.53; H, 6.92; N, 21.36. Found: C, 59.68; H, 6.90; N, 21.43.
3g	164 [a]	83	3169 1683 1644	1.0 (t, 3H, CH_3), 1.4 (t, 3H, N-C-CH_3), 1.7 (m, 2H, CH_2), 2.7 (t, 2H, CH_2), [2.0 (br s, 3H), 2.8 (br s, 1H), 3.6 (br s, 2H), 4.1 (br d, 1H pyrrolidine protons)], 4.4 (q, 2H, N-CH_2), 9.8 (br s, 1H, NH)	276	Calcd: C, 60.85; H, 7.30; N, 20.28. Found: C, 60.96; H, 7.31; N, 20.32.
6a	297 [b]	84	3292 1698 1672 1691	1.0 (t, 3H, CH_3), 1.7 (m, 2H, CH_3), 2.5 (t, 2H, CH_2), 4.0 (s, 3H, N-CH_3), 7.6 (br s, 1H, NH), 10.5 (br s, 1H, NH)	236	Calcd: C, 50.84; H, 5.12; N, 23.72. Found: C, 50.93, H, 5.11; N, 23.79.
6b	265 [c]	80	3253 1691 1662 1623	1.0 (t, 3H, CH_3), 1.4 (t, 3H, N-C-CH_3), 1.6 (m, 2H, CH_2), 2.4 (t, 2H, CH_2), 4.3 (m, 2H, N-CH_2), 7.5 (br s, 1H, NH), 10.1 (br s, 1H, NH)	250	Calcd: C, 52.79; H, 5.64; N, 22.39. Found: C, 52.90; H, 5.62; N, 22.44.

Solvent used for recrystallization: [a] ethyl acetate:*n*-hexane; [b] methanol:ethyl acetate; [c] methanol.

Scheme 3



EXPERIMENTAL

^{1}H and ^{13}C nmr spectra were recorded on a Varian Gemini (300 and 100 MHz respectively) nmr spectrometer at ambient temperature using TMS as internal standard. Mass spectrometry (70 eV) was carried out on a Perkin-Elmer Hitachi RMU-6 L instrument. IR spectra were obtained in KBr pellets on a Shimadzu 435 instrument. Elemental Analysis was carried out on Perkin-Elmer 2400 S CHN analyzer. Melting points were determined in capillaries using Polman digital melting point apparatus (Model-mp-96). Reagents and solvents were of analytical grade. Solvents were dried before use.

2-(1-Alkyl-4-nitro-3-*n*-propyl-1*H*-pyrazolyl-5-carboxamido)-substituted Carboxylic Acids (**2a-g**).

General Procedure.

A mixture of 1-alkyl-4-nitro-3-*n*-propyl pyrazolyl-5-carboxylic acid **1a/1b** [8] (0.01 mol) and thionyl chloride (10 mL) in benzene (10 mL) was refluxed for 3 h. The reaction mixture was cooled and excess thionyl chloride was removed *in vacuo*. The oily residue was dissolved in benzene (10 mL) and this acid chloride was cautiously added to the appropriate α-amino acid (0.011 mol) in 10% aq. KOH solution (20 mL) at 10-20 °C and reaction mixture was stirred for 15 min. The organic layer was separated

and aqueous layer was acidified with 2 *N* HCl (10 mL) and extracted with ethyl acetate (2 x 25 mL). Ethyl acetate solution was dried (Na_2SO_4), concentrated and the resulting carboxylic acid derivative 2 was recrystallised from ethyl acetate/hexane.

1-Alkyl-6-substituted-3-*n*-propyl-1,4,5,6,7,8-hexahydropyrazolo-[4,3-*e*][1,4]diazepin-5,8-diones (**3a-g**).

General Procedure.

To a solution of **2** (5 mmol) in methanol (25 mL) was added Raney nickel (0.5 g) and reaction mixture was placed under a hydrogen atmosphere (75 psi) in a Paar hydrogenation apparatus for 4-5 h, and then filtered through a celite bed. The catalyst was washed with methanol (15 mL) and combined filtrates were evaporated to dryness *in vacuo*. The resulting residue was taken in H_2O (20 mL) and extracted with ethyl acetate (3 x 25 mL). The organic extracts were combined, dried (Na_2SO_4) and evaporated under reduced pressure to give the corresponding pyrazolodiazepine dione derivative **3a-g** which was recrystallised from appropriate solvent.

2-(4-Amino-1-methyl-3-*n*-propyl-1*H*-pyrazolyl-5-carboxamido) Acetic Acid (**4**).

To a solution of 2-(1-methyl-4-nitro-3-*n*-propyl-1*H*-pyrazolyl-5-carboxamido) acetic acid **2a** (2.7 g, 5 mmol) in methanol (25 mL), was added Raney nickel (0.5 g) and reaction mixture was placed under a hydrogen atmosphere at atmospheric pressure for 4 h and then filtered through a celite bed. The catalyst was washed with methanol (10 mL) and the combined filtrates were evaporated to dryness *in vacuo*. The resulting residue was taken in water (25 mL) and extracted with chloroform (3 x 25 mL). The organic extracts were combined, dried (Na_2SO_4) and evaporated under reduced pressure. Recrystallisation of the residue from benzene gave compound **4**, yield 72%, m.p.124 °C. MS: m/e 240 M^+; IR (KBr, cm^{-1}) 3510, 3366, 3234, 1727, 1646; ^1H NMR ($CDCl_3$): δ 1.0 (t, 3H, CH_3), 1.65 (m, 2H, CH_2), 2.6 (t, 2H, CH_2), 3.8-4.2 (br m, 7H, N-CH_3, N-CH_2, NH_2), 8.8 (s, 1H, NH).

Cyclisation of 2-(4-Amino-1-methyl-3-*n*-propyl-1*H*-pyrazolyl-5-carboxamido) Acetic Acid (**4**).

A solution of **4** (0.01 mol) and catalytic amount of 4-dimethylamino pyridine in dichloromethane (20 mL) was cooled to 0 °C. Solution of DCC (2.06 g, 0.01 mol) in dichloromethane was added drop wise to the above solution over a period of 10 min while maintaining the temperature at 0-5 °C. After the addition, the solution was stirred for an additional period of 5 min and the temperature was allowed to rise to room temperature over a period of 1 h. Separated urea derivative was filtered, washed with dichloromethane (15 mL), combined organic layers were washed with water, dried (Na_2SO_4) and evaporated *in vacuo*. The residue was triturated with *n*-hexane and the resulting solid was recrystallised from ethyl acetate to give pyrazolo[4,3-*e*][1,4]diazepin-5,8-dione derivative **3a**, yield 68%, m.p. 199 °C.

1-Methyl/ethyl-3-*n*-propyl-1,4,5,6,7,8-hexahydropyrazolo[4,3-*e*]-[1,4]diazepin-5,6,8-trione (**6a/b**).

General Method.

To a solution of 4-amino-1-alkyl-3-*n*-propyl pyrazolyl-5-carboxamide **5a/b** (0.01 mol) in dichloromethane (40 mL) and pyridine (2 mL), oxalyl chloride (1.3 g, 0.011 mol) was added drop wise and reaction mixture was stirred at room temperature for 3 h. 1-Alkyl-3-*n*-propyl-1,4,5,6,7,8-hexahydropyrazolo[4,3-*e*][1,4]-diazepin-5,6,8-trione 6a/b separated out from the clear solution, which was collected by filtration, washed with water (2 x 30 mL) and recrystallised from suitable solvent.

REFERENCES AND NOTES

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[1] J. A. Vida, Medicinal Chemistry, Part III, M. W. Wolf, I. W. Burger, John Wiley & Sons, New York 1981, pp. 787.

[2] F. J. Tinney, J. P. Sanchez and J. A. Noas, *J. Med. Chem*., **17**, 624 (1974).

[3] A. Edenhofer, *Helv. Chem. Acta*., **58**, 2192 (1975).

[4] L. Fontanella, L. Mariani, G. Tarzia and N. Corsico, *Eur. J. Med. Chem*., **11**, 217 (1976).

[5] R. Jaunin, *Helv. Chem. Acta*., **57**, 1934 (1974).

[6] H. A. DeWald, I. C. Nordin, Y. J. L' Italien and R. F. Parcel, *J. Med. Chem*., **16**, 1346 (1973).

[7] H. A. DeWald , S. Lobbestael and B. P. H. Poschel, *J. Med. Chem*., **24**, 982, (1981).

[8] J. Fray, D. J. Bull, K. Cooper, M. J. Parry and M. H. Stefaniak, *J. Med. Chem*., **38**, 3524 (1995).