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Synthesis of 2-Azabicyclo[3.1.0]hexane Tricarboxylate and its Transformation into a New Proline-γ-acetic Acid Equivalent

Loredana Arenare,[a] Paolo De Caprariis,[a] Maura Marinozzi,[b] Benedetto Natalini,[b] Roberto Pellicciari *[b]

[a] Dipartimento di Chimica Farmaceutica e Tossicologica, Università degli Studi di Napoli "Federico II", Via D. Montesano, 49, 80131 Napoli

[b] Istituto di Chimica Farmaceutica e Tecnica Farmaceutica, Università degli Studi di Perugia, Via del Liceo, 1, 06123 Perugia

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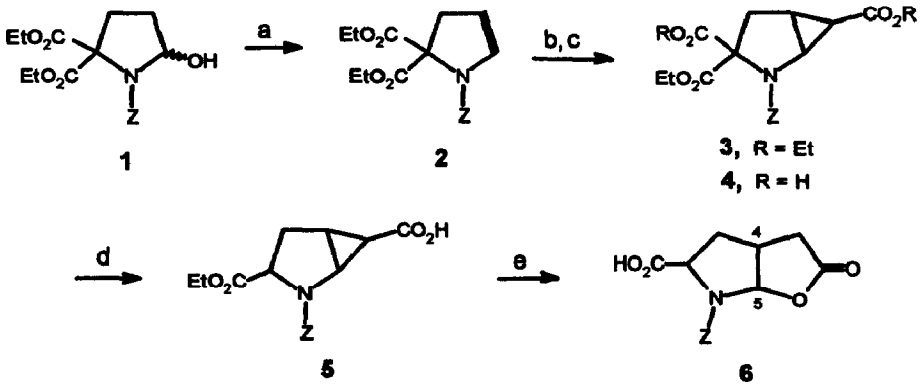
Abstract: *The synthesis of the 2-azabicyclo[3.1.0]hexane derivative* **3** *together with its transformation into 2-carboxy-4-carboxymethyl-pyrrolidin-5-ol lactone* (**6**)*, a useful proline derivative is described.*

In connection with a continuing interest in the synthesis and biological evaluation of non proteinogenic amino acid analogues[1] we report herein the preparation of 2-azabicyclo- [3.1.0]hexane tricarboxylate (**3**), a versatile synthon incorporating the proline moiety, useful for new synthetic elaborations of this important amino acid. The preparation of the title compound as well as its transformation into 2-carboxy-4-carboxymethyl-pyrrolidin-5-ol lactone (**6b**) is depicted in Scheme I.

Scheme I



a) P_2O_5, C_6H_6, reflux, 2 h; b) EDA, $Rh_2(OAc)_4$, CH_2Cl_2, rt, 12 h; c) 0.5N NaOH (H_2O-MeOH 1.4:1), rt, 5 h; d) toluene, reflux, 12 h; e) 6N HCl (H_2O-dioxane 5:1), rt, 72 h.

Condensation of diethyl N-benzyloxycarbonylaminomalonate with acrolein in a benzenic solution of sodium ethoxide gave diethyl N-benzyloxycarbonyl-5-hydroxy-pyrrolidine-2,2-dicarboxylate (**1**, 82% yield)[2] which was then dehydrated by treatment with P_2O_5 in benzene to give the corresponding diethyl N-benzyloxycarbonyl-2,3-dihydropyrrole-2,2-dicarboxylate (**2**) in 35% yield. Dirhodium(II)tetraacetate catalyzed decomposition of ethyl diazoacetate (EDA) in the presence of **2** (CH_2Cl_2, 12 h, rt; EDA:**2**:cat = 40:10:1) afforded the cyclopropylpyrrolidine tricarboxylate **3**[3] as *ca.* 1:1 mixture of *exo* and *endo* forms in 46% yield.[4] Partial hydrolysis of the homoenamine-type derivative **3** with 0.5N NaOH (H_2O-MeOH 1.4:1) for 5 h at room temperature afforded the corresponding diacid **4** (85% yield) which was refluxed in toluene for 12 h to give the 4,5-cyclopropylproline derivative **5** in 75% yield. When **5** was submitted to acidic treatment (6N HCl, water-dioxane 5:1) for 72 h at room temperature, it was transformed into the corresponding 2-carboxy-4-carboxymethyl-pyrrolidin-5-ol lactone (**6**) in 87% yield.[5] The *cis* relative stereochemistry of C-5 hydrogen to C-4 hydrogen in **6** was evident from the magnitude of the coupling constant (J=5.3 Hz). Synthetic applications of the lactone **6**, a proline-γ-acetic acid equivalent, as well as new elaborations of the 4,5-cyclopropylproline dicarboxylate **5** are currently under study.

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References and Notes

1. a) Pellicciari, R.; Natalini, B.; Luneia, R.; Marinozzi, M.; Roberti, M.; Rosato, G. C.; Sadeghpour, B. M.; Snyder, J. P.; Monahan, J. B.; Moroni, F. *Med. Chem. Res.* **1992**, *2*, 491-496; b) Franceschetti, L.; Garzon-Aburbeh, A.; Mahmoud, M. R.; Natalini, B.; Pellicciari, R. *Tetrahedron Lett.* **1993**, *34(19)*, 3185-3188.
2. Yoshioka, T.; Watanabe, A.; Isshiki, K.; Fukagawa, Y.; Ishikura, T. *Tetrahedron Lett.*, **1986**, *27(36)*, 4335-4338.
3. **3**: ^{1}H-NMR ($CDCl_3$) δ 1.30 (9H, m, 3x $CH_2\underline{CH_3}$); 1.90 and 2.20 (2H, 2xm, 3-CH_2); 2.75 (1H, m, 4-CH); 2.95 (1H, 2d, J=7 Hz, $\underline{CH}CO_2Et$); 3.95-4.35 (7H, m, 3x $\underline{CH_2}CH_3$ and 5-CH); 5.15 (2H, 2s, $\underline{CH_2}Ph$); 7.30 (5H, m, aromatic's).
4. For previous examples, see: a) Wenkert, E.; Alonso, M. E.; Gottlieb, H. E.; Sanchez, E. L.; Pellicciari, R.; Cogolli, P. *J. Org. Chem.*, **1977**, *42*, 3945-3948; b) Wenkert, E.; Hudlicky, T. *J. Org. Chem.* **1988**, *53*, 1953-7.
5. **6**: mp 97-99 °C; IR ($CHCl_3$) ν_{max} 1781, 1717 cm^{-1}; ^{1}H-NMR (500 MHz, $CDCl_3$) δ 1.90-2.10 and 2.30-2.50 (2H, 2xm, 3-C-H_2), 2.55 (1H, m, 4-C-H), 2.75 and 3.10 (2H, 2xm, CH_2CO), 4.55 (1H, m, 2-C-H), 5.20 (2H, s, $\underline{CH_2}Ph$), 6.10 (1H, 4xd, J=5.3 Hz, 5-C-H), 6.90 (1H, br s, CO_2H), 7.30 (5H, br s, aromatic H's); ^{13}C-NMR ($CDCl_3$) δ 33.61 and 34.14 (C-3), 34.78 and 34.93 ($\underline{CH_2}CO$), 36.58 and 37.69 (C-4), 59.67 and 60.29 (C-2), 68.10 ($\underline{CH_2}Ph$), 91.68, 92.00 and 92.58 (C-5), 127.75, 127.88, 128.00, 128.26, 128.55 and 135.47 (aromatic C's), 154.00 (N-CO), 174.39 (CO), 175.54 (CO_2H).

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