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REACTION OF 2,6-DI(BROMOMETHYL)-1,4-DIHYDROPYRIDINE WITH β-ALANINE

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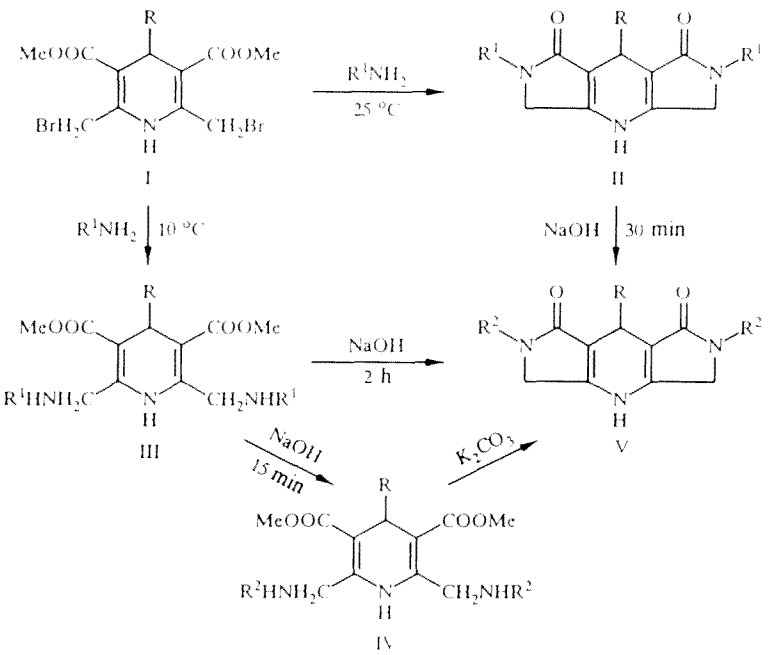
We have found that the reaction of 2,6-di(bromomethyl)- 3,5-dimethoxycarbonyl-4-(2-difluoromethoxyphenyl)-1,4-dihydropyridine (I) with β-alanine ethyl ester at room temperature gives a 46% yield of a tricyclic compound, i.e., the derivative of 1,3,4,5,7,8-hexahydro(dipyrrolo)[3′,4′-b;3,4-e]pyridine (II). If the reaction was conducted at a lower temperature, the nucleophilic substitution product (III) was isolated with a yield of 65%. Alkaline hydrolysis of the ester groups in the β-alanine residue of compound (III) and brief treatment with a 1 N solution of sodium hydroxide led to the production of compound (IV) with a yield of 63%. More prolonged saponification led to intramolecular cyclization and the formation of the lactam (V) with a yield of 75%. Compound can also be obtained by alkaline hydrolysis of compound (II) or as a result of the cyclization of compound (IV) in an alkaline medium at room temperature.



R = $C_6H_4OCHF_2$-*o*, R^1 = CH_2CH_2COOEt, R^2 = CH_2CH_2COOH

2,6-Di[(2-ethoxycarbonyl)ethyl]-8-(2-difluoromethoxyphenyl)-1,7-dioxo-1,3,4,5,7,8-hexahydro(dipyrrolo)[3′,4′-b;3,4-e]pyridine (II) ($C_{26}H_{29}F_2N_3O_7$). mp 160-162°C. PMR spectrum (deuterochloroform) (δ, ppm): 1.20 (6H, t, $\underline{CH_3}CH_2$), 2.52 (4H, m, CH_2CO), 3.52 (4H, m, NCH_2), 3.85 (4H, s, 3,5-CH_2), 4.08 (4H, q, $\underline{CH_2}CH_3$), 5.13 (1H, s, 8-H), 6.95-7.03 (4H, m, H_{arom}), 7.07 (1H, t, J = 75 Hz, CHF_2), 9.21 (1H, bs, NH).

2,6-Di[(2-ethoxycarbonylethyl)aminomethyl]-3,5-dimethoxycarbonyl-4-(2-difluoromethoxyphenyl)-1,4-dihydropyridine (III) ($C_{28}H_{37}F_2N_3O_9$). mp 69-70°C. PMR spectrum (deuterochloroform) (δ, ppm): 1.23 (6H, t, $\underline{CH_3}CH_2$), 1.77 (2H, bs, $CH_2\underline{NH}$), 2.53 (4H, t, CH_2CO), 2.90 (4H, t, CH_2N), 3.60 (6H, s, OCH_3), 4.06 (4H, s, 2,6-CH_2), 4.22 (4H, q, $\underline{CH_2}CH_3$), 5.37 (1H, s, 4-H), 6.52 (1H, t, J = 75 Hz, CHF_2), 6.90-7.50 (4H, m, H_{arom}), 9.58 (1H, bs, NH).

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2,6-Di[(2-carboxyethyl)aminomethyl]-3,5-dimethoxycarbonyl-4-(2-difluoromethoxyphenyl)-1,4-dihydropyridine (IV) ($C_{24}H_{29}F_2N_3O_9$). mp 116-119 °C. PMR spectrum (deuterochloroform + DMSO-d_6) (δ, ppm): 2.52 (8H, m, $COCH_2$, COOH, CH_2NH), 3.56 (4H, m, CH_2N), 3.64 (6H, s, OCH_3), 3.94 (4H, s, 2,6-CH_2), 5.13 (1H, s, 4-H), 6.97 (1H, t, J = 75 Hz, CHF_2), 6.86-7.46 (4H, m, H_{arom}), 9.22 (1H, bs, NH).

2,6-Di(2-carboxyethyl)-8-(2-difluoromethoxyphenyl)-1,7-dioxo-1,3,4,5,7,8-hexahydro(dipyrrolo)[3′,4′-b;3,4-e]pyridine (V) ($C_{22}H_{21}F_2N_3O_7$). mp 193-195°C. PMR spectrum (DMSO-d_6) (δ, ppm): 2.39 (4H, m, CH_2CO), 3.43 (4H, m, CH_2N), 4.03 (4H, s, 3,5-CH_2), 4.87 (1H, s, 8-H), 6.90-7.40 (4H, m, H_{arom}), 7.28 (1H, t, J = 75 Hz, CHF_2), 9.87 (1H, bs, NH), 12.23 (2H, bs, COOH).