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SYNTHESIS AND REACTIONS OF 4-AMINO-3-CARBETHOXY-1,2-DIHYDROSPIRO(NAPHTHALENE-2,1′-CYCLOPENTANE)

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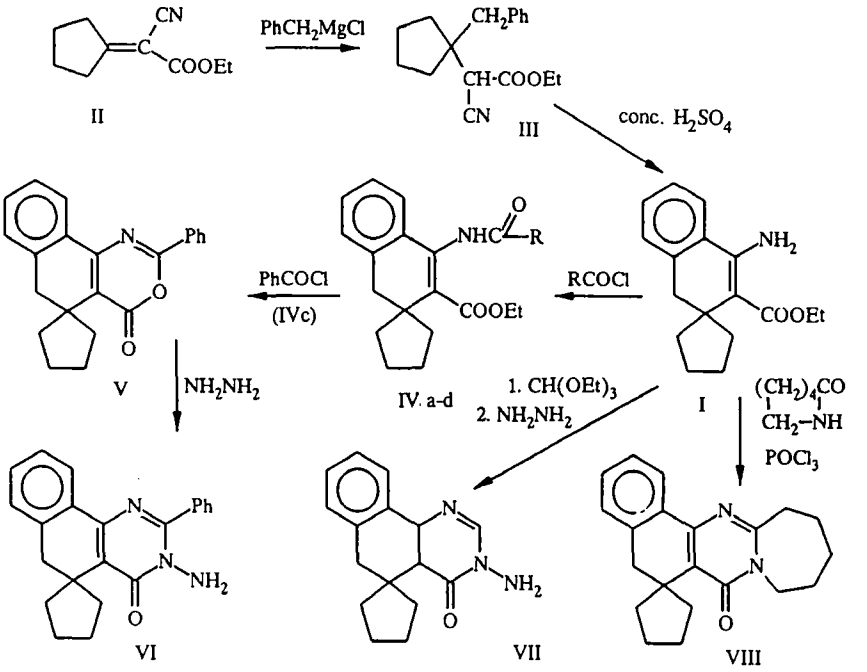
Addition of benzylmagnesium chloride to cyclopentylidenecyanoacetic ester gives 1-benzyl-1-(cyanocarbethoxymethyl)cyclopentane and this can be cyclized to 4-amino-3-carbethoxy-1,2-dihydrospiro-(naphthalene-2,1′-cyclopentane). Acylation of the obtained aminoester with carboxylic acid chlorides produces the corresponding amides (which can react with an excess of benzoyl chloride). It can also react with orthoformic ester. In both cases the product can then react with hydrazine hydrate. Treatment of the same aminoester with caprolactam gives a tetrahydrospiro(benzo[h]quinazoline-5,1′-cyclopentane) derivative.

We have developed a method for synthesis of 4-amino-3-carbethoxy-1,2-dihydrospiro(naphthalene-2,1′-cyclohexane) [1] which was later put through a series of interesting reactions [2, 3] extending the work to an investigation of aminoester syntheses. In this report we describe the preparation and reactions of the novel β-aminoester, 4-amino-3-carbethoxy-1,2-dihydrospiro(naphthalene-2,1′-cyclopentane) (I).

Compound I was prepared from cyclopentylidenecyanoacetic ester (II). Treatment of the latter with benzylmagnesium chloride occurs exclusively at the ethylene bond to give 1-benzyl-1-(cyanocarbethoxymethyl)cyclopentane (III). Cyclization of cyanoester III in concentrated sulfuric acid gives the desired product I.



IV a R = Et, b R = Pr, c R = Ph, d R = CH_2Ph

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Aminoester I is a weak nucleophile and does not take part in nucleophilic substitution reactions with alkyl halides, benzyl chloride, or propargyl bromide. It reacts smoothly in refluxing benzene with propionic, butyric, benzoic, and phenylacetic acid chlorides to give the corresponding amides (IVa-d). When aminoester I is acylated with excess benzoyl chloride and the reaction time increased to 25 h, amide IVc undergoes an intramolecular cyclization to give benzoxazine V. Refluxing the latter with hydrazine hydrate gives the 3,4,5,6-tetrahydrospiro(benzo[h]quinazoline-5,1′-cyclopentane) VI. Starting from ester I we have synthesized other derivatives of this tetracyclic system. Thus, reaction with orthoformic ester and subsequent condensation of the intermediate ethoxymethylene compound with hydrazine hydrate gives the amine VII. Aminoester I and caprolactam in the presence of phosphorus oxychloride give the pentacyclic derivative VIII.

EXPERIMENTAL

IR Spectra were recorded on a UR-20 instrument (in Vaseline oil) and PMR spectra on a Varian T-60 using TMS or HMDS as internal standard. Mass spectra were obtained on an MX-1320 spectrometer with direct introduction of the sample into the ion source and ionization voltage of 70 eV. TLC was carried out on Silufol UV-254 plates and revealed using iodine vapor.

1-Benzyl-1-(cyanocarbethoxymethyl)cyclopentane III. A solution of ester II (70 g, 0.39 mole) in ether (250 ml) was added dropwise with stirring at 25-30°C to a solution of benzylmagnesium chloride obtained from magnesium (14.4 g, 0.6 mole) and benzyl chloride (76 g, 0.6 mole) in absolute ether (300 ml). The reaction mixture was stirred at room temperature for 5 h and hydrochloric acid (10%, 250 ml) was added dropwise at 10-15°C with stirring until complete decomposition of the complex. The organic layer was separated, washed with water, and dried over magnesium sulfate. After distillation of ether the residue was distilled *in vacuo* to give product III (87 g, 82%) with bp 195°C/9 mm and n_D^{20} 1.5210. IR Spectrum: 1605 (C=C arom.), 1740 (C=O), 2260 cm^{-1} (C≡N). PMR Spectrum ($CDCl_3$): 1.13 (3H, t, J = 7 Hz, $OCH_2\underline{CH_3}$); 1.36-1.90 (8H, m, $4CH_2$); 2.71 (2H, s, CH_2Ph); 3.37 (1H, s, CH); 4.1 (2H, q, J = 7 Hz, OCH_2); 6.93-7.40 ppm (5H, m, H_{arom}). Found, %: C 75.39; H 7.68; N 5.00. $C_{17}H_{21}NO_2$. Calculated, %: C 75.24; H 7.80, N 5.16.

4-Amino-3-carbethoxy-1,2-dihydrospiro(naphthalene-2,1′-cyclopentane) (I). Concentrated sulfuric acid (30 ml) was added dropwise with stirring at 2-7°C to cyanoester III (15 g, 0.055 mole). The mixture was stirred at 10-15°C for 7 h and poured onto ice. The precipitated mass was separated, treated with ammonia solution, and extracted with ether. The ether extract was washed with water and dried over magnesium sulfate. After distillation of solvent the residue crystallized. The crystals were washed with 70% alcohol and dried in air to give I (7 g, 74%) with mp 80-82°C. IR Spectrum: 1600 (C=C arom.); 1640 (C=C); 1710 (C=O), 3300, 3450 cm^{-1} (NH_2). PMR Spectrum ($CDCl_3$): 1.33 (3H, t, J = 7 Hz, $OCH_2\underline{CH_3}$); 1.10-2.16 (8H, m, $4CH_2$); 2.70 (2H, s, 1-CH_2); 4.13 (2H, q, J = 7 Hz, OCH_2); 6.37 (2H, br. s, NH_2); 7.00-7.60 ppm (4H, m, H_{arom}). Found, %: C 75.11, H 7.95; N 5.28. $C_{17}H_{21}NO_2$. Calculated, %: C 75.24; H 7.80; N 5.16.

4-Acylamino-3-carbethoxy-1,2-dihydrospiro(naphthalene-2,1′-cyclopentanes) (IVa-d). A mixture of aminoester I (5.4 g, 0.02 mole), the acid chloride (0.02 mole), and benzene (30 ml) was refluxed with a condenser for 4 h. After distillation of solvent, recrystallization of the residue gave product IV.

Amide IVa. Yield 79%. mp 148-150°C (ethanol–water, 2:1). R_f 0.49 (ethyl acetate–nonane, 2:1). IR Spectrum: 1605 (C=C arom.), 1655 (C=O amide), 1700 (C=O), 3230 cm^{-1} (NH). PMR Spectrum (CCl_4): 0.80-2.20 (13H, m, $4CH_2$, COC_2H_5); 1.30 (3H, t, J = 7 Hz, $OCH_2\underline{CH_3}$); 2.30 (2H, s, 1-CH_2); 4.20 (2H, q, J = 7 Hz, OCH_2); 6.80-7.40 (4H, m, H_{arom}); 8.40 ppm (1H, br. s, NH). Found, %: C 73.20; H 7.93; N 4.42. $C_{20}H_{25}NO_3$. Calculated, %: C 73.37, H 7.70; N 4.28.

Amide IVb. Yield 80%. mp 147-149°C (ethanol–water, 2:1). R_f 0.59 (ethyl acetate–nonane, 2:1). IR Spectrum: 1605 (C=C arom.); 1660 (C=O amide); 1700 (C=O); 3220 cm^{-1} (NH). PMR Spectrum: (CD_3OD): 0.86-2.53 (15H, m, $4CH_2$, COC_3H_7); 1.30 (3H, t, J = 7 Hz, $OCH_2\underline{CH_3}$); 2.76 (2H, s, 1-CH_2); 4.23 (2H, q, J = 7 Hz, OCH_2); 7.20 ppm (4H, m, H_{arom}). Found, %: C 74.01; H 8.16; N 4.27. $C_{21}H_{27}NO_3$. Calculated, %: C 73.87; H 7.97 N 4.10.

Amide IVc. Yield 27%. mp 169-171°C (ethanol–water, 2:1). R_f 0.55 (ether–benzene, 1:3). IR Spectrum: 1610 (C=C arom.); 1650 (C=O amide); 1705 (C=O); 3230 cm^{-1} (NH). PMR Spectrum ($CDCl_3$); 1.23 (3H, t, J = 7 Hz, $OCH_2\underline{CH_3}$); 1.40-2.23 (8H, m, $4CH_2$); 2.80 (2H, s, 1-CH_2); 4.23 (2H, q, J = 7 Hz, OCH_2); 7.00-8.17 (9H, m, H_{arom}); 8.6 ppm (1H, br. s, NH). Found, %: C 76.90; H 6.96; N 3.65. $C_{24}H_{25}NO_3$. Calculated, %: C 76.77; H 6.71; N 3.73.

Amide IVd. Yield 54%. mp 165-167°C (ethanol–water, 2:1). R_f 0.40 (ethyl acetate–hexane, 1:1). IR Spectrum: 1600 (C=C arom.); 1650 (C=O amide); 1700 (C=O); 3230 cm^{-1} (NH). PMR Spectrum ($CDCl_3$); 1.17 (3H, t, J = 7 Hz, $OCH_2\underline{CH_3}$); 1.58 (8H, m, $4CH_2$); 2.50 (2H, s, 1-CH_2); 3.57 (2H, s, $\underline{CH_2}Ph$); 4.07 (2H, q, J = 7 Hz, OCH_2); 6.97 (4H, m, H_{arom}); 7.20 (5H, m, H_{arom}); 7.37 ppm (1H, br. s, NH). Found, %: C 76.90; H 7.17; N 3.88. $C_{25}H_{27}NO_3$. Calculated, %: C 77.08; H 6.99; N 3.60.

4-Oxo-2-phenyl-5,6-dihydrospiro(benzo[*h*]-3,1-benzoxazine-5,1′-cyclopentane) (V). A mixture of aminoester I (5.4 g, 0.02 mole), benzoyl chloride (5.6 g, 0.04 mole), and benzene (30 ml) were refluxed with a condenser for 25 h. After distillation of benzene the residue was recrystallized from ethanol to give the benzoxazine V (3.8 g, 58%) with mp 139-141°C. R_f 0.52 (ethyl acetate–nonane, 1:3). IR Spectrum: 1605 (C=C arom.); 1720 cm^{-1} (C=O). PMR Spectrum (acetone-D_6): 1.23-2.53 (8H, m, $4CH_2$); 2.83 (2H, s, 6-CH_2); 6.93-8.56 ppm (9H, m, H_{arom}). Found, %: C 80.03; H 5.87; N 4.36. $nC_{22}H_{19}NO_2$. Calculated, %: C 80.22; H 5.81; N 4.25.

3-Amino-4-oxo-2-phenyl-3,4,5,6-tetrahydrospiro(benzo[*h*]quinazoline-5,1′-cyclopentane) (VI). A mixture of oxazine V (3.3 g, 0.01 mole), hydrazine hydrate (1 g, 0.02 mole), and absolute ethanol (10 ml) was refluxed with a condenser for 7 h. The product was cooled and the precipitated crystals filtered and recrystallized from dioxane–water (2:1) to give the aminoquinazoline VI (1.8 g, 52%) with mp 188-190°C and R_f 0.61 (ethyl acetate–nonane, 2:1). IR Spectrum: 1600 (C=C arom.); 1640 (C=O); 3200, 3280 cm^{-1} (NH_2). PMR Spectrum ($CDCl_3$): 1.17-2.60 (8H, m, $4CH_2$); 2.87 (2H, s, 6-CH_2); 5.17 (2H, s, NH_2); 7.00-8.40 ppm (9H, m, H_{arom}). Found, %: C 77.07; H 6.05, N 12.39. $C_{22}H_{21}N_3O$. Calculated, %: C 76.94; H 6.16; N 12.24.

3-Amino-4-oxo-3,4,5,6-tetrahydrospiro(benzo[*h*]quinazoline-5,1′-cyclopentane) (VII). A mixture of the aminoester I (4.1 g, 0.015 mole), orthoformic ester (10.4 g; 0.07 mole), 5-6 drops of acetic anhydride, and benzene (20 ml) was refluxed with a condenser for 7 h. The solvent and excess orthoformate were distilled off and hydrazine hydrate (4 g, 0.08 mole) in absolute ethanol (20 ml) was added. The product was refluxed with a condenser for 5 h. The crystals formed on cooling were filtered, washed with cold ethanol, and recrystallized from benzene to give the quinazoline VII (2 g, 50%) with mp 210-211°C and R_f 0.45 (ether–benzene, 2:1). IR Spectrum: 1605 ($C=C_{arom}$); 1640 (C=O); 3180, 3310 cm^{-1} (NH_2). PMR Spectrum ($CDCl_3$): 1.10-2.50 (8H, m, $4CH_2$); 2.83 (2H, s, 6-CH_2); 4.87 (2H, br. s, NH_2); 7.00-8.17 (4H, m, H_{arom}); 8.27 ppm (1H, s, CH). Mass spectrum, *m/z* (*I*, %): M^+ 267 (100), 238 (41), 236 (12), 225 (52), 224 (27), 221 (34), 209 (13), 196 (37), 182 (12), 180 (11), 167 (10), 166 (14), 152 (12), 141 (11), 128 (10), 114 (12), 95 (11) Found, %: C 72.02; H 6.60; N 15.64. $C_{16}H_{17}N_3O$. Calculated, %: C 71.89; H 6.41; N 15.72.

7-Oxo-2,3,4,5,7,9-hexahydro-1H,7H-spiro(benzo[h]azepino[2,1-b]quinazoline-9,1′-cyclopentane) (VIII). Phosphoryl chloride (2 ml) was added at 5-10°C to a solution of caprolactam (2.5 g, 0.022 mole) in dry dichloroethane (10 ml). The temperature of the reaction mixture was raised to 35-40°C, stirred for 10 min, and the aminoester I (5.7 g, 0.021 mole) in dichloroethane (15 ml) was added. The product was refluxed with stirring for 6 h, cooled, a solution of sodium acetate (2.5 g) in water (15 ml) added, and refluxing continued for a further 20 min. The organic layer was separated and the aqueous extracted with dichloroethane. The combined extracts and organic layer were washed with water and dried with magnesium sulfate. After distillation of solvent the residue was recrystallized from ethanol–water (3:1) to give azepine VIII (1 g, 15%) with mp 128-130°C and R_f 0.52 (ethyl acetate–hexane, 1:2). IR Spectrum: 1600 (C=C arom.); 1655 cm^{-1} (C=O). PMR Spectrum ($CDCl_3$): 1.10-2.50 (14H, m, $7CH_2$); 2.77 (2H, s, 9-CH_3); 3.00 (2H, m, 1-CH_2); 4.27 (2H, m, N–CH_2); 7.00-8.20 ppm (4H, m, H_{arom}). Mass spectrum, *m/z* (*I*, %): M^+ 320 (100); 292 (18); 291 (54); 279 (12); 278 (71); 277 (21); 236 (7); 235 (6); 224 (6); 180 (5); 140 (5); 139 (6); 96 (6). Found, %: C 78.89; H 7.57; N 8.93. $C_{21}H_{24}N_2O$. Calculated, %: C 78.71; H 7.55; N 8.74.

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