Michael Additions to Acrylonitrile, Methyl Acrylate and Methyl Vinyl Ketone to N_b-Benzylidenetryptophan Methyl Ester

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Michael addition to methyl acrylate and methyl vinyl ketone of N_b-benzylidene-L-tryptophan methyl ester **1** gave 2-(3-indolylmethyl)glutamic dimethyl ester **2a** and α-(3-oxobutyl)tryptophan methyl ester **2b** respectively. Addition to acrylonitrile of **1** yielded α,N_a-dicyanoethyltryptophan methyl ester **3**.

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Several authors [1-3] have reported the use of Schiff base ester of α-amino acids as a general synthon for the synthesis of α-alkyl and α-functionalized α-amino acids. In connection with this approach, Michael addition of Schiff base ester of α-amino acids is a method to effect alkylation of amino acids derivatives at their α-carbon [1].

Our investigations concerning the synthesis of new tryptophan derivatives [2-6] led us to examine in this paper the Michael additions to acrylonitrile, methyl acrylate, methyl vinyl ketone and ethyl 3-aminocrotonate of N_b-benzylidene-L-tryptophan methyl ester.

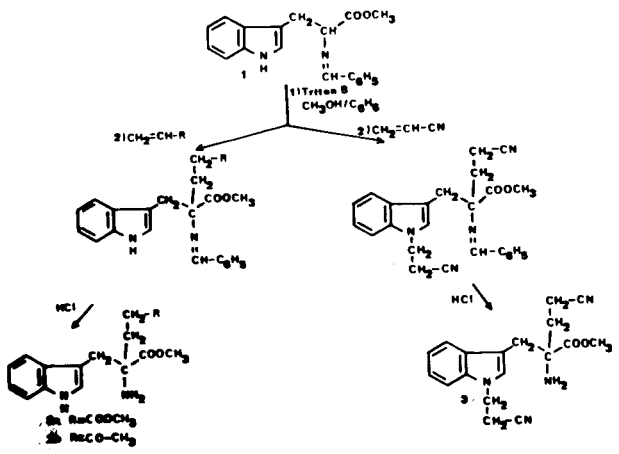
Reaction of N_b-benzylidene-L-tryptophan methyl ester **1** [2,7] with methyl acrylate and methyl vinyl ketone in equilibrating conditions (catalytic amount of triton B in methanol/benzene), followed by acidic hydrolysis gave rise to the formation of 2-(3-indolylmethyl)glutamic dimethyl ester **2a** and α-(3-oxobutyl)tryptophan methyl ester **2b** respectively. The structural assignments were based on the spectral data.

When **1** was treated with acrylonitrile and catalytic amount of triton B in methanol/benzene, α,N_a-dycyanoethyltryptophan methyl ester was obtained **3**. No α-cyanoethyltryptophan methyl ester was formed. Compound **3** was established on the basis of elemental analysis and spectral data.

Finally in the reaction of **1** with ethyl 3-aminocrotonate, the Michael addition compound was not formed and the N_b-benzylidene-L-tryptophan methyl ester was recovered.

These results could be easily explained by the different electrophilic [8] character between ethyl 3-aminocrotonate, methyl acrylate or methyl vinyl ketone, and acrylonitrile.

Scheme



EXPERIMENTAL

Melting points were measured with a Büchi apparatus and are uncorrected. The ir spectra were determined on a Perkin-Elmer 781 spectrophotometer. The ^1H and ^{13}C nmr spectra were recorded on a Varian T-60A (60 MHz) and Varian FT-80A spectrometers, respectively. Mass spectrometry was performed with a Varian MAT-711 apparatus. The elemental analyses were performed by "Centro Nacional de Química Orgánica", Madrid.

General Procedure.

To a solution of **1** (0.01 mole) in 25 ml of benzene and 25 ml of methanol was added benzyltrimethylammonium hydroxide solution about 40% in methanol (40 drops) under nitrogen. The mixture was stirred for 1 hour and the reagent (0.01 mole) was then added and stirred for an additional thirty minutes. The solvent was evaporated under reduced pressure and the resulting oil was solved in chloroform and washed with water. The chloroform layer was dried (magnesium sulfate) and evaporated under reduced pressure. The resulting oil was treated with 1*N* hydrochloric acid (25 ml) for 1 hour at room temperature. The reaction mixture was washed with ethyl ether, and the aqueous phase was neutralized with saturated sodium bicarbonate solution, extracted with chloroform and dried over magnesium sulfate. The solvent was evaporated under reduced pressure providing an oil. Trituration with ethyl acetate gave the compound.

2-(3-Indolylmethyl)glutamic Dimethyl Ester (**2a**).

This compound was obtained in a yield of 50%, mp 173-175° (ethyl acetate); ir (potassium bromide): ν 3220, 3190 (NH_2), 3120 (NH), 1730, 1680 (C=O), 1610 (ArC=C) cm^{-1}; ^1H nmr (DMSO-d_6): δ 1.9-2.8 (m, 6H, $2CH_2$, NH_2), 3.2 (s, 2H, CH_2-indole), 3.5 (s, 3H, CH_3), 3.8 (s, 3H, CH_3), 6.9-7.7 (m, 5H, ArH), 8.1 (s-broad, 1H, NH); ^{13}C nmr (DMSO-d_6): δ 29.1, 29.4, 31.1 (CH_2), 51.3, 51.6 (CH_3), 63.4 (C_α), 107.7, 112.2, 117.9, 118.6, 121.5, 125.7, 127.6, 136.6 (indole), 172.9, 174.4 (C=O); ms: m/e (relative intensity) 304 (M^+), 130 (M^+-$C_7H_{12}NO_4$, 100).

Anal. Calcd. for $C_{16}H_{20}N_2O_4$: C, 63.15; H, 6.57; N, 9.22. Found: C, 63.44; H, 6.36; N, 9.38.

α-(3-Oxobutyl)tryptophan Methyl Ester (**2b**).

This compound was obtained in a yield of 30%, mp 92-94° (ethyl acetate); ir (potassium bromide): ν 3400, 3340 (NH_2), 3160 (NH), 1730,

1710 (C=O), 1610, 1600 (ArC=C) cm^{-1}; ^1H nmr (deuteriochloroform): δ 2.0 (s, 3H, CH_3), 2.7-3.3 (m, 8H, $3CH_2$, NH_2), 3.7 (s, 3H, OCH_3), 6.9-7.5 (m, 5H, ArH), 8.5 (s-broad, 1H, NH).

Anal. Calcd. for $C_{16}H_{20}N_2O_3$: C, 66.64; H, 6.99; N, 9.71. Found: C, 66.89; H, 7.02; N, 9.40.

α,N_a-Dicyanoethyltryptophan Methyl Ester (**3**).

This compound was obtained in a yield of 60%, mp 96-98° (ethyl acetate); ir (potassium bromide): ν 3380, 3300 (NH_2), 2260 (C≡N), 1720 (C=O), 1600 (ArC=C) cm^{-1}; ^1H nmr (DMSO-d_6): δ 1.8-3.1 (m, 10H, $4CH_2$, NH_2), 3.5 (s, 3H, CH_3), 4.4 (t, 2H, CH_2-N-indole), 6.9-7.6 (m, 5H, ArH); ^{13}C nmr (DMSO-d_6): δ 11.7, 18.5, 34.2, 35.9, 41.1 (CH_2), 51.8 (CH_3), 61.1 (C_α), 108.8, 109.7, 118.8, 118.9 (indole), 119.1, 120.6 (C≡N), 121.3, 127.5, 128.4, 135.5 (indole), 175.2 (C=O); ms: m/e (relative intensity) 324 (M^+), 183 (M^+-$C_6H_9N_2O_2$, 100).

Anal. Calcd. for $C_{18}H_{20}N_4O_2$: C, 66.64; H, 6.21; N, 17.27. Found: C, 66.75; H, 6.51; N, 17.03.

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