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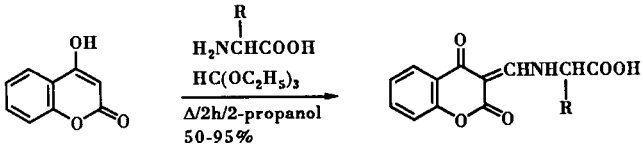
Received May 20, 1992

A new series, the *N*-(methylene-4-oxocoumarinyl)aminoacids were synthesized by condensation of 4-hydroxycoumarin with α-aminoacids in the presence of excess ethyl orthoformate.

J. Heterocyclic Chem., **29**, 1817 (1992).

We have previously reported results on the condensation of 4-hydroxycoumarin with substituted ureas [1] and carbamates [2] in the presence of ethyl orthoformate giving good yields of the corresponding 3-ureidomethylene coumarins and *N*-(methylene-4-oxocoumarinyl)carbamates. Since the coumarin ring forms part of many heterocyclic compounds of pharmacological interest [3-6], these derivatives are being evaluated for potential biological activity. We were therefore interested in linking this structure to other molecules of biological importance such as the α-aminoacids. Such derivatives would have a bifunctional structure [7], which in common with the previously studied compounds incorporates a primary amino group that may condense with the coumarin ring, as well as a carboxylic acid group which can be transformed into esters, acid chlorides and other derivatives. Furthermore, the polyfunctional nature of some aminoacids enables synthesis of more complex molecules of potential biological interest.

We selected various commercially available, natural (L)-aminoacids $RCH(NH_2)$-COOH including those: substituted with an alkyl group (glycine, alanine, leucine); substituted with an aromatic group (phenylalanine, tyrosine, tryptophane, L-Dopa) and substituted with a functional group such as an alcohol (serine), thiol (cysteine), acid (glutamic acid), and amine (glutamine).



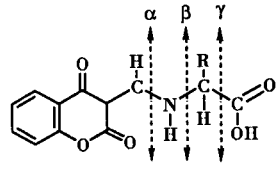
1 R = H
2 R = CH_3
3 R = $CH_2CH(CH_3)_2$
4 R = $CH_2C_6H_5$
5 R = $CH_2C_6H_4OH$
6 R = $CH_2C_6H_3(OH)_2$
7 R = CH_2-indolyl
8 R = CH_2OH
9 R = CH_2SH
10 R = $(CH_2)_2CONH_2$
11 R = $(CH_2)_2COOH$

Refluxing an equimolar ratio of 4-hydroxycoumarin and the (L)-α-aminoacid in 2-propanol in the presence of excess ethyl orthoformate led to a new series of compounds, the corresponding *N*-(methylene-4-oxocoumarinyl)aminoacids.

The reaction was rapid, and we did not observe any competition from the intermolecular condensation of 4-hydroxycoumarin [8]. All the products were obtained as solids, and their purities were checked by thin layer chromatography (eluent = dichloromethane/methanol, 10/1 v/v). Their structures were determined by elemental analysis, ^1H nmr and mass spectrometry.

The ^1H nmr spectra displayed split doublets between 10.35 and 11.95 ppm and between 7.57 and 8.62 ppm attributed to the NH and ethylenic protons respectively. The splitting was due to the existence of *Z* and *E* isomers, which was observed in our previous studies [1,2], and has been reported for other compounds with the same ethylenic structure [9].

Mass spectrometry showed, apart from the molecular ion peak, and fragments of the coumarin ring [10], fragments due to cleavage of the side chain: α-cleavage with loss of an amino acid moiety; β-cleavage with loss of a hydrocarbon chain; γ-cleavage with loss of a CO_2H(M^+-45); or loss of the R group (M^+-R).



This condensation reaction provides a good route to *N*-coumarinyl substituted α-aminoacids from the corresponding L-aminoacids. With the D-aminoacids only the yield was altered. For example the reaction with D-alanine under the same conditions as for the L-form led to an in-

creased yield (75%) of the corresponding *N*-substituted derivative **12** in an equally rapid reaction. Thus the nature of the configuration of the aminoacid did not affect condensation with 4-hydroxycoumarin. Encouraging results have been obtained in a study of the reactivity of these substituted α-aminoacids, and their potential biological activity is also under investigation.

EXPERIMENTAL

Melting points were determined in an Electrothermal apparatus. The ^{1}H nmr spectra were recorded on a Bruker AC 80 instrument (solvent DMSO-d_6), and mass spectra on a Nermag R 1010 spectrometer (70 eV, electron impact). Elemental analysis was carried out at the Inter-University microanalysis center in Toulouse. The aminoacids, 4-hydroxycoumarin and ethyl orthoformate were obtained from Janssen, Fluka and Aldrich.

N-(Methylene-4-oxocoumarinyl)aminoacids.

A stirred solution of 4-hydroxycoumarin (1.62 g, 0.01 mole), ethyl orthoformate (2.25 g, 0.015 mole), L- or D-aminoacid (0.01 mole) in 2-propanol (30 ml) was refluxed for 2 hours. The precipitate which formed hot or on cooling to room temperature was collected, washed with 2-propanol and then recrystallized.

N-(Methylene-4-oxocoumarinyl)glycine **1**.

This compound was crystallized from dimethylformamide-water (yield = 95%), mp 232-233°; ^{1}H nmr: δ 4.43 (d, 2H, CH_2), 7.22-8.00 (m, 4H, ar), 8.52 (dd, 1H, CH, *Z* and *E*), 10.35 and 11.65 (dd, 1H, NH, *Z* and *E*); ms: (m/z, %) 247 (M^+, 1), 201 (1), 202 (0.5), 189 (0.5), 188 (3.5), 175 (1), 174 (0.5), 173 (0.5), 121 (5), 120 (3), 93 (6), 92 (19), 73 (94), 43 (15), 42 (81), 41 (73), 30 (100).

Anal. Calcd. for $C_{12}H_9NO_5$: C, 58.30; H, 3.64; N, 5.66. Found: C, 58.06; H, 3.67; N, 5.70.

N-(Methylene-4-oxocoumarinyl)alanine **2**.

This compound was crystallized from dimethylformamide-water (yield = 50%), mp 244-245°; ^{1}H nmr: δ 1.55 (d, 3H, CH_3), 4.68 (m, 1H, CH), 7.18-7.97 (m, 4H, ar), 8.58 (dd, 1H, CH, *Z* and *E*), 10.42 and 11.94 (dd, 1H, NH, *Z* and *E*); ms: (m/z, %) 261 (M^+, 11), 217 (1), 216 (6), 215 (2), 189 (2), 188 (5), 175 (2), 174 (2), 173 (2), 122 (7), 121 (11), 120 (2), 93 (6), 92 (2), 74 (19), 73 (100), 44 (93), 43 (13), 42 (28), 41 (27), 30 (29).

Anal. Calcd. for $C_{13}H_{11}NO_5$: C, 59.77; H, 4.21; N, 5.36. Found: C, 59.98; H, 4.26; N, 5.25.

N-(Methylene-4-oxocoumarinyl)leucine **3**.

This compound was crystallized from ethanol-water (yield = 80%), mp 165-166°; ^{1}H nmr: δ 0.92 (d, 6H, CH_3), 1.72 (m, 1H, CH), 1.76 (dd, 2H, CH_2), 4.65 (m, 1H, CH), 7.22-8.00 (m, 4H, ar), 8.62 (dd, 1H, CH, *Z* and *E*), 10.39 and 11.88 (dd, 1H, NH, *Z* and *E*); ms: (m/z, %) 303 (M^+, 47), 259 (10), 258 (57), 257 (2), 246 (2), 189 (5), 188 (17), 175 (23), 174 (7), 173 (14), 164 (17), 121 (46), 120 (13), 93 (14), 92 (33), 84 (29), 77 (25), 69 (40), 67 (23), 56 (23), 55 (71), 53 (52), 45 (27), 44 (36), 43 (100), 39 (46), 31 (28).

Anal. Calcd. for $C_{16}H_{17}NO_5$: C, 63.36; H, 5.61; N, 4.62. Found: C, 62.98; H, 5.75; N, 4.80.

N-(Methylene-4-oxocoumarinyl)phenylalanine **4**.

This compound was crystallized from dimethylformamide-water (yield = 55%), mp 226-227°; ^{1}H nmr: δ 3.32 (m, 2H, CH_2), 4.95 (m, 1H, CH), 7.20-7.95 (m, 9H, ar), 8.37 (dd, 1H, CH, *Z* and *E*), 10.35 and 11.53 (dd, 1H, NH, *Z* and *E*); ms: (m/z, %) 337 (M^+, 61), 293 (5), 292 (9), 291 (5), 246 (100), 191 (24), 189 (4), 188 (4), 175 (50), 174 (2), 173 (6), 121 (41), 120 (5), 93 (10), 92 (20), 91 (82), 77 (19), 65 (18).

Anal. Calcd. for $C_{19}H_{15}NO_5$: C, 67.65; H, 4.45; N, 4.15. Found: C, 67.54; H, 4.51; N, 4.13.

N-(Methylene-4-oxocoumarinyl)tyrosine **5**.

This compound was crystallized from ethanol-water (yield = 55%), mp 210-211°; ^{1}H nmr: δ 3.16 (d, 2H, CH_2), 4.86 (m, 1H, CH), 6.62-7.98 (m, 8H, ar), 8.32 (dd, 1H, CH, *Z* and *E*), 10.32 and 11.83 (dd, 1H, NH, *Z* and *E*); ms: (m/z, %) 353 (M^+, 6), 308 (2), 247 (30), 246 (3), 200 (10), 199 (32), 189 (3), 188 (4), 175 (7), 174 (3), 173 (4), 163 (10), 162 (14), 121 (33), 120 (20), 107 (59), 93 (9), 92 (22), 77 (32), 65 (23), 63 (21), 57 (23), 55 (24), 53 (18), 45 (30), 44 (100), 43 (36), 42 (27), 41 (28), 39 (25), 31 (45), 30 (25).

Anal. Calcd. for $C_{19}H_{15}NO_6$: C, 64.58; H, 4.24; N, 3.96. Found: C, 64.26; H, 4.17; N, 3.82.

N-(Methylene-4-oxocoumarinyl)-L-dopa **6**.

This compound was crystallized from ethanol-water (yield = 70%), mp 170-171°; ^{1}H nmr: δ 3.05 (m, 2H, CH_2), 4.80 (m, 1H, CH), 6.35-6.68 (m, 3H, ar), 7.20-7.98 (m, 4H, ar), 8.32 (dd, 1H, CH, *Z* and *E*), 11.38 and 11.79 (dd, 1H, NH, *Z* and *E*); ms: (m/z, %) 369 (M^+, 5), 325 (0.5), 247 (10), 199 (22), 189 (2), 188 (2), 175 (3), 174 (1), 162 (19), 121 (17), 120 (17), 93 (4), 92 (16), 77 (16), 63 (15), 44 (100), 31 (18).

Anal. Calcd. for $C_{19}H_{15}NO_7$: C, 61.79; H, 4.06; N, 3.79. Found: C, 61.37; H, 4.23; N, 3.69.

N-(Methylene-4-oxocoumarinyl)tryptophan **7**.

This compound was crystallized from ethanol-water (yield = 80%), mp 193-194°; ^{1}H nmr: δ 3.40 (d, CH, CH_2), 4.94 (m, 1H, CH), 6.93-7.92 (m, 8H, ar), 8.33 (dd, 1H, CH, *Z* and *E*), 10.40 and 11.90 (dd, 1H, NH, *Z* and *E*), 10.96 (s, 1H, NH); ms: (m/z, %) 376 (M^+, 1), 189 (2), 188 (1), 175 (1), 173 (0.5), 162 (9), 130 (66), 121 (22), 120 (28), 117 (67), 93 (10), 92 (48), 77 (21), 73 (30), 65 (18), 64 (23), 63 (37), 62 (16), 44 (100), 39 (22).

Anal. Calcd. for $C_{21}H_{16}N_2O_5$: C, 67.02; H, 4.25; N, 7.44. Found: C, 66.94; H, 4.26; N, 7.39.

N-(Methylene-4-oxocoumarinyl)serine **8**.

This compound was crystallized from ethanol-water (yield = 50%), mp 194-195°; ^{1}H nmr: δ 3.92 (d, 2H, CH_2), 4.72 (m, 1H, CH), 7.20-8.00 (m, 4H, ar), 8.62 (dd, 1H, CH, *Z* and *E*), 10.53 and 12.01 (dd, 1H, NH, *Z* and *E*); ms: (m/z, %) 277 (M^+, 50), 259 (27), 232 (12), 189 (17), 188 (65), 175 (42), 174 (14), 173 (29), 162 (26), 121 (100), 120 (44), 93 (22), 92 (54), 77 (24), 73 (28), 69 (21), 65 (25), 64 (21), 63 (28), 55 (24), 53 (31), 45 (43), 44 (51), 43 (26), 39 (24), 31 (65).

Anal. Calcd. for $C_{13}H_{11}NO_6$: C, 56.31; H, 3.97; N, 5.05. Found: C, 56.59; H, 3.98; N, 5.11.

N-(Methylene-4-oxocoumarinyl)cysteine **9**.

This compound was crystallized from 2-propanol-hexane (yield = 70%), mp 145° dec; ^{1}H nmr: δ 3.26 (d, 2H, CH_2), 4.91 (m, 1H, CH), 7.20-7.95 (m, 4H, ar), 8.60 (dd, 1H, CH, *Z* and *E*), 10.50 and 11.90 (dd, 1H, NH, *Z* and *E*); ms: (m/z, %) 293 (M^+, 0.1), 248 (0.3), 247 (0.3), 246 (0.2), 189 (4), 188 (3), 175 (1), 174 (1), 173 (3), 121 (16), 120 (10), 93 (9), 92 (27), 86 (100), 59 (45), 58 (18), 45 (25), 44

(76).

Anal. Calcd. for $C_{13}H_{11}NO_5S$: C, 53.24; H, 3.75; N, 4.77. Found: C, 53.60; H, 4.02; N, 4.75.

N-(Methylene-4-oxocoumarinyl)glutamine **10**.

This compound was crystallized from dimethylformamide-ethanol (yield = 90%), mp 203-204°; ^{1}H nmr: δ 2.17 (m, 4H, CH_2), 4.64 (m, 1H, CH), 7.20-8.00 (m, 4H, ar), 8.57 (dd, 1H, CH, *Z* and *E*), 10.41 and 11.89 (dd, 1H, NH, *Z* and *E*); ms: (m/z, %) 318 (M^+, 1), 189 (34), 188 (11), 162 (11), 121 (38), 120 (29), 93 (13), 92 (71), 85 (12), 83 (14), 69 (39), 68 (29), 65 (36), 64 (56), 63 (75), 62 (23), 57 (34), 56 (71), 55 (63), 54 (32), 53 (45), 51 (35), 50 (28), 45 (100), 44 (80), 43 (54), 42 (29), 41 (30), 40 (28), 39 (88), 38 (32), 32 (34), 31 (75), 30 (28).

Anal. Calcd. for $C_{15}H_{14}N_2O_6$: C, 56.60; H, 4.40; N, 8.80. Found: C, 56.30; H, 4.70; N, 8.65.

N-(Methylene-4-oxocoumarinyl)glutamic Acid **11**.

This compound was crystallized from water (yield = 60%), mp 223-224°; ^{1}H nmr: δ 2.28 (m, 4H, CH_2), 4.65 (m, 1H, CH), 7.22-7.97 (m, 4H, ar), 7.57 (dd, 1H, CH, *Z* and *E*), 10.37 and 11.87 (dd, 1H, NH, *Z* and *E*); ms: (m/z, %) 319 (M^+, 24), 260 (28), 228 (12), 217 (1), 216 (3), 215 (2), 190 (18), 189 (11), 188 (23), 175 (14), 174 (1), 173 (1), 162 (28), 121 (100), 120 (35), 93 (14), 92 (33), 84 (14).

Anal. Calcd. for $C_{15}H_{13}NO_7$: C, 56.42; H, 4.07; N, 4.38. Found: C, 56.30; H, 4.19; N, 4.41.

N-(Methylene-4-oxocoumarinyl)-D-alanine **12**.

This compound was crystallized from dimethylformamide-water (yield = 80%), mp 244-245°; ^{1}H nmr: δ 1.55 (d, 3H, CH_3), 4.70 (m, 1H, CH), 7.21-8.00 (m, 4H, ar), 8.60 (dd, 1H, CH, *Z* and *E*), 10.50 and 11.90 (dd, 1H, NH, *Z* and *E*); ms: (m/z, %) 261 (M^+, 4), 217 (1), 216 (3), 215 (2), 189 (0.5), 188 (3), 175 (1), 174 (1), 173 (1), 121 (4), 120 (2), 93 (1), 92 (2), 44 (100), 42 (53).

Anal. Calcd. for $C_{13}H_{11}NO_5$: C, 59.77; H, 4.21; N, 5.36. Found: C, 59.70; H, 4.18; N, 5.39.

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