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Spectral Study of some *N*-Acyldipeptides and their Derivatives

S. S. SANDHU*, JASWINDER SINGH and SANJAY SHARMA

Department of Chemistry, Guru Nanak Dev University, Amritsar-148 005

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The *N*-acyldipeptides, such as (*N*-formyl, *N*-acetyl, *N*-benzoyl, *N*-chloroacetyl, *N*-trifluoroacetyl)-L-phenylalanylglycine, and their ethylesters were prepared and characterised. The effect of different substituents on a particular group have been studied using ^{13}C nmr spectral data.

N-protected dipeptides are of great interest because they are present in albumin, mosaic virus and natural proteins. *N*-Benzoyl-, *N*-formyl-, *N*-acetyl-, *N*-chloroacetyl-, *N*-trifluoroacetyl-dipeptides can be used as the starting material in the preparation of transition metal complexes which mimic natural macromolecules. A search of literature shows that (*N*-formyl, *N*-acetyl, *N*-benzoyl)-L-phenylalanylglycine and *N*-benzoyl-dl-alanylglycine and their ethyl esters are known[1-6]. These were prepared by known method. *N*-Chloroacetyl protected dipeptides, as new compounds, were prepared by using the similar method.

Experimental

The reported procedure of *N*-trifluoroacetyl protected dipeptide by using thiophenylesters of *N*-trifluoroacetylamino acids[7] had the following limitations. (i) the reaction performed at low temperature (−30 to −35°), (ii) requirement of longer time (20 h) for completion and dipeptides requiring at least 2 days, (iii) long chain peptides could not be synthesised, and (iv) alternatively, preparation of trifluoroacetylpeptides by indirect method requiring costlier materials and number of steps[8]. Hence, we have used other method[1] for the synthesis of *N*-trifluoroacetyl protected dipeptides which could be obtained at 0−5° in 5−6 h.

N-Acetyl-dl-valylglycine and its ethyl ester have been reported for the first time. Spectral data are not available in literature for any of these protected dipeptides and their ethyl esters.

(*N*-Formyl, *N*-acetyl, *N*-chloroacetyl, *N*-trifluoroacetyl)-L-phenylalanylglycine and their ethyl esters along with *N*-acetyl-dl-valylglycine and its ethyl ester were prepared by the method as reported[1] for the *N*-formyl-L-phenylalanylglycine and *N*-formyl-L-phenylalanylglycine ethyl ester.

N-Benzoyl-L-phenylalanylglycine ethyl ester : To *N*-benzoyl-L-phenylalanine (2.69 g) and glycine ethyl ester (1.03 g) in anhydrous tetrahydrofuran was added *N*-ethoxycarbonyl-2-ethoxy-1,2-dihydroquinoline (EEDQ) (2.47 g). The mixture was stirred for 8−10 h at room temperature. The solvent was then removed under reduced pressure and the residue was crystallised from ethyl acetate and potroleum ether to yield the product, m.p. 147−48°[9].

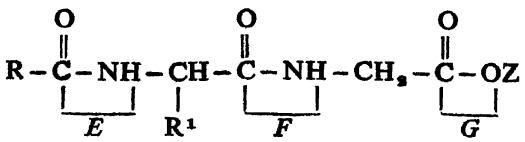
N-Benzoyl-dl-alanylglycine ethyl ester : It was prepared by the same method as has been mentioned in the case of *N*-benzoyl-L-phenylalanylglycine ethyl ester (m.p. 108°).

N-Benzoyl-L-phenylalanylglycine (m.p. 163−65°) and *N*-benzoyl-dl-alanylglycine (m.p. 161°)[6] were obtained by hydrolysis[1] of their corresponding ethyl esters.

All *N*-acyldipeptide and their esters were characterised by m.p., ir, ^{13}C nmr and mass spectral data. Purity of the compounds was also checked by thin layer chromatography.

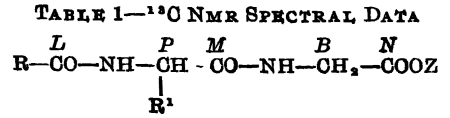
Results and Discussion

All the dipeptide esters and dipeptides have common amide (*E*), peptide (*F*) and carboxylate (*G*) groups.



1; R=H, $R^1=CH_2C_6H_5$, Z=CH_2CH_3
2; R=H, $R^1=CH_2C_6H_5$, Z=H
3; $R=CH_3$, $R^1=CH_2C_6H_5$, Z=CH_2CH_3
4; $R=CH_3$, $R^1=CH_2C_6H_5$, Z=H
5; $R=CH_2Cl$, $R^1=CH_2C_6H_5$, Z=CH_2CH_3
6; $R=CH_2Cl$, $R^1=CH_2C_6H_5$, Z=H
7, $R=CF_3$, $R^1=CH_2C_6H_5$, Z=CH_2CH_3
8; $R=CF_3$, $R^1=CH_2C_6H_5$, Z=H
9; $R=CH_3$, $R=CH(CH_3)_2$, Z=CH_2CH_3
10, $R=CH_3$, $R^1=CH(CH_3)_2$, Z=H
11; $R=C_6H_5$, $R^1=CH_2C_6H_5$, Z=CH_2CH_3
12, $R=C_6H_5$, $R^1=CH_2C_6H_5$, Z=H
13; $R=C_6H_5$, $R^1=CH_3$, Z=CH_2CH_3
14; $R=C_6H_5$, $R^1=CH_3$, Z=H

TABLE 1—^{13}C NMR SPECTRAL DATA



Compd. no.	R	*L* CO	*P* CH	*M* CO	*B* CH_2	*N* CO
1	—	161.16	52.80	169.56	41.29	171.06
2	—	160 85	52.22	170.04	42.25	171.19
3	22.97	169.38	54.40	170.31	41.44	171.68
4	22.54	169.21	53.84	171.12	41.45	171.85
5	38.39	166.38	54.62	169.33	42.44	170.99
6	38.94	166.90	55.26	—	43.71	172.26
7	24.99	157.68	54.87	169.28	41.66	170.11
8	—	—	—	—	—	—
9	23.20	170.07	58.50	170.27	41.33	171.73
10	21.25	174.60	62.81	176.43	42.88	179.07
11	—	169 45	54.80	169.45	41.47	171.71
12	—	171.21	54.86	166.45	41.52	171.94
13	—	167.23	49.17	169.53	41.37	172.74
14	—	167.23	48.78	171.12	41.59	172.73

All the dipeptide esters showed similar ir spectra which show bands at 3 380–3 270 (NH stretch), 1 720–1 750 and 1 375–1 410 (COO stretch), 1 600–1 680 cm^{-1} (amide-I) and 1 532–1 560 cm^{-1} (amide-II). N-Protected dipeptide esters can be differentiated from their acids by the appearance of a new band at 2 500–2 740 cm^{-1} (OH stretching of hydrogen bonded COOH group) in case of dipeptide acids.

General structural formula of compounds is presented in Table 1 along with the ^{13}C nmr spectral data. In ^{13}C nmr spectra, carbonyl carbon adjacent to R in compounds **1** and **2** (where R=H) shows peak at 161.16 and 160.85 ppm respectively. The electron density at this carbon can be affected by inductive effect and resonance effect. Where inductive effect dominates resonance effect, the electron-withdrawing groups should shift the peak of adjacent carbon downfield and electron-donating groups upfield But where resonance effect dominates inductive effect, the reverse should be true. On replacement of H with electron-donating group CH_3 (in **3**, **4**, **9** and **10**), the carbonyl carbon shows downfield shift to 169.21–174.60 ppm which indicates that resonance effects are contributing more. On replacing H with electron-withdrawing phenyl group (in **11**–**14**) or $ClCH_2$ group (in **5** and **6**) this carbon again shows downfield shift to 167.23–171.21 ppm (in **11**–**14**) and 166.38–166.90 ppm (in **5** and **6**). But replacement of H with CF_3 group (in **7** and **8**) shows on upfield signal. Thus phenyl and $ClCH_2$ groups participate through inductive effect, whereas CF_3 and CH_3 groups participate through resonance effect. The presence of Cl (in **5** and **6**) results in upfield shift for respective C-atom. The side chain CH absorbs at 31.10 and 32.98 ppm while CH(*P*) absorbs at 54.50 and 52.22 ppm in **9** and **10** respectively (low field in comparison to CH of side chain). In the present study the magnitude of chemical shift is in the expected order of inductive effects of different groups attached to CH(*P*). The electron impact spectra of all the N-protected dipeptides and their ethyl esters have been recorded. The molecular ion peak corresponds to the molecular weight. Compounds **3**, **4**, **5** and **6** show the base peak at *m/e* 120 corresponding to the fragment $NH_2CHCH_2C_6H_5$. Compounds **7**, **8** and **2** show the base peak at *m/e* 91 corresponding to fragment $CH_2C_6H_5$ while a peak at *m/e* 105 is observed due to C_6H_5CO fragment in **11**, **12**, **13** and **14**. In **1** the NHCHCO group shows base peak at *m/e* 56, while in **9** and **10** the base peak due to $NH_2CHCH(CH_3)_2$ is observed at *m/e* 72.

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