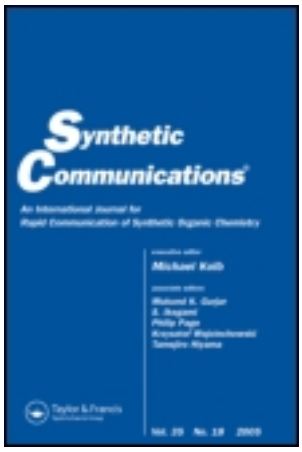

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PREPARATION OF *N*-ACYL DERIVATIVES OF AMINO ACIDS FROM ACYL CHLORIDES AND AMINO ACIDS IN THE PRESENCE OF CATIONIC SURFACTANTS. A VARIATION OF THE SCHOTTEN-BAUMANN METHOD OF BENZOYLATION OF AMINO ACIDS

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ABSTRACT

A very efficient method for the preparation of *N*-acylamino acids from the corresponding acyl chloride and amino acid is described. Amino acids, potassium carbonate, acyl chloride, and a catalytic amount of cationic surfactants were mixed in tetrahydrofuran and refluxed without ever obtaining a clear reaction mixture. After hot filtration, the product was isolated from the hot tetrahydrofuran solution in very high or almost quantitative yields.

INTRODUCTION

The preparation of *N*-acyl derivatives of simple aliphatic amines and amides is well established in organic synthesis (1). The treatment of acyl halides with

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ammonia or amines is a very general reaction for the preparation of amides (2). The reaction is highly exothermic and must be carefully controlled, usually by cooling the reaction mixture or performing the reaction in a very dilute solution. In all of these reactions, a base must be present to react with the liberated hydrochloric acid. In not performing this step, two equivalents of the amine are required. Because the reaction of an acyl chloride with an amine is much faster by comparison to the hydrolysis of the acyl chloride, an aqueous alkali can be used as a base. This modification of the reaction is called the Schotten-Baumann procedure (3–5). In the Schotten-Baumann method of benzoylation, the amino compound, or its salt, is dissolved or suspended in a slight excess of an 8–15% sodium hydroxide solution. A small excess (about 10–15% more than the theoretical quantity) of benzoyl chloride is then added and the mixture is vigorously shaken or stirred. Benzoylation proceeds smoothly and the product (*N*-benzoyl derivative) usually separates as a solid. The sodium hydroxide hydrolyzes the excess of benzoyl chloride, yielding sodium benzoate and sodium chloride, which remains in solution. The benzoyl compounds frequently include traces of unchanged benzoyl chloride, which thus escape hydrolysis by sodium hydroxide. It is advisable wherever possible to recrystallize, or to simply wash the crystals with alcohol (either methanol or ethanol) because this solvent will dissolve benzoyl chloride, and the ester that should form is soluble in alcohol.

N-acylation of amines can be accomplished with acid anhydrides (2). The scope and mechanism of this reaction is similar to the method of preparation with acyl chloride, except the reaction is much slower, and, in the case of aromatic amines (anilines), the reaction requires slight heat. If the corresponding ester of an acid and amine are used for the acylation of an amine, the reaction usually requires an acid catalyst and extended heating of the reaction mixture. The least desirable method of preparation of amides is directly from amines and acids (6). According to this procedure, the mixture of an acid and an amine should be heated for a short time (∼30 min) at elevated temperatures (if possible above 160°C). Although preparation of amides in this way is very simple and solvent is not required, there are two major disadvantages: both the acid and amine, as well as the product must be thermally stable and their boiling points should be above 200°C. If one of the reactant components is not thermally stable, then there are several alternative reagents for activating the carboxylic acid, such as N,N'-dicyclohexylcarbodamine (7–9), 1,1′-carbonyldiimidazole (1), and *N*-acyltetrazole (10–12).

RESULTS AND DISCUSSION

Recently, we have demonstrated that *N*-acyl derivatives of amino acids and small peptides are good differentiation agents for various cancer cells (13–15). Preparation of a wide variety of *N*-acyl derivatives of amino acids is desirable.

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First of all, the preparation of amides of amino acids is not as simple as it is for simple aliphatic and aromatic amines. Amino acids are in Zwitterionic form and that makes them quite insoluble in the majority of organic solvents. Certainly, there are many methods that are currently used for the preparation of *N*-acyl derivatives of amino acids and peptides (16–19). They all require several steps, including protection of the carboxylic acid group of the amino acid, activation of the carboxylic amino acid group of the product acyl moiety, and finally, deprotection of *N*-acylamino acid carboxylic group.

One of the methods that we initially used for the preparation of *N*-acyl derivatives of amino acids is through the acylation of the amino acid ester. Amino acid esters were prepared from amino acids and ethanol (around twenty equivalents) with a 1.1 equivalent of sulfuric acid. The prepared mixture was refluxed for several hours, ethanol was evaporated, and the oily residue was dissolved in chloroform and carefully poured over potassium carbonate. The release of carbon dioxide and mixing of the chloroform mixture and solid potassium carbonate should be gradual. After the release of carbon dioxide stopped, the chloroform solution was separated from solid and evaporated to an oily residue. According to the ^{1}H-NMR, the ester is more than 97% pure and can be used without further purification.

The esters *N*-acylation were performed in chloroform solution with two equivalents of the aminoacid ester and one equivalent of acid chloride. The reaction was instantaneously over. The chloroform solution was extracted with aqueous hydrochloric acid and sodium hydroxide, affording a pure *N*-acylamino acid ester. The *N*-acylamino acid ester was then hydrolyzed with an equivalent amount of aqueous sodium hydroxide and *N*-acylamino acid was isolated following common procedures for ester hydrolysis (1). This procedure gives acceptable yields (around 35–40% in regards to the amino acid or 70–85% in regards to an acyl chloride). Furthermore, if various chloroformates are used as sources for the preparation of *N*-hydroxyurea derivatives of amino acids, the yields are even lower due to their hydrolysis in the course of the amino acid ester hydrolysis.

To avoid several steps in the *N*-acylamino acid, preparation we decided to perform direct *N*-acylation of the amino acid with acids under the conditions of the Schotten-Baumann method. Amino acids were dissolved in equivalent amounts of aqueous sodium hydroxide and the corresponding acyl chloride was added. In this method, the amino acid is fully transferred to its sodium salt and is soluble in water. In the course of the reaction, water-soluble sodium chloride and insoluble *N*-acylamino acid should be formed. The product should be collected by simple filtration. In our attempts to optimize this method for the preparation of *N*-benzoylmethionine and *N*-benzoylalanine, we always obtained a mixture of benzoic acid, product, and the corresponding amino acid that requires separation through crystallization or simple chromatography on silica gel with ethyl acetate as an eluate. The yields are around 50–60%. It seems that the presence

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of amino acid actually catalyzes the hydrolysis of the acyl chloride in water media.

Considering the fact that acyl chlorides hydrolyze very fast in moist solvents, one can assume that, for the successful reaction between an acyl chloride and an amino acid, water should be eliminated from the reaction media. We have successfully used micellar media in the past to perform many organic reactions (25,26). As a surfactant, dodecyltriammonium bromide was used. The yields for this reaction seem to be slightly higher than direct *N*-acylation in water media. We have also used reverse micelles to bring the nucleophile from solid state into organic media through the formation of reverse micelles (20–26).

Initially, we mixed equivalent amounts of potassium carbonate and amino acids with 1% of dodecyltriammonium bromide as a surfactant and chloroform as a solvent. A small amount of water (5 mL) was added in chloroform (200 mL) to form the reverse micelle. Into this suspension, an equivalent amount of benzoyl chloride was added. The reaction was refluxed overnight, chloroform was separated, evaporated, and the product crystallized. In the case of methionine and benzoyl chloride, only 20–30% of product was isolated. The idea was to bring the amino acid potassium salt into chloroform solution (actually in reverse micelle) and allow it to react with acyl chloride. It seems that chloroform has too low a polarity to accomplish this task. Chloroform was substituted with the more polar tetrahydrofuran. All solvents and reagents were used without prior drying, so there was a sufficient amount of water present to allow reverse micelles to form. Only catalytic amounts of surfactant ($\sim$1%) were used for the reaction. In this case, almost quantitative yields of the *N*-acylamino acid derivatives were obtained.

We believe that the mechanism of the reaction is one that we have described previously for some other reactions in reverse micelles (25,26). The Zwitterionic amino acid was partially transferred in its sodium salt, releasing in this way its amino group as a nucleophile for the reaction with the acyl chloride that is in the tetrahydrofuran solution. Then the sodium cation in the amino acid salt was substituted with dodecyltrimethylammonium cation, making a new amino acid salt that is soluble in tetrahydrofuran. Now both reagents were in the same media and formation of the amide bond was possible. The formed *N*-acylamino acid remained in tetrahydrofuran solution, while the newly formed surfactant (now as dodecyltrimethylammonium chloride) reacted with another molecule of amino acid sodium salt of the amino acid that resides in solid phase, similar to the phase transfer catalysis (27,28). In this way, formation of the *N*-acyl product after refluxing overnight was more than 90%. Products were usually soluble in hot tetrahydrofuran and were isolated from the reaction suspension through the separation of the hot tetrahydrofuran solution from the solid residue and evaporation of tetrahydrofuran until an oily or solid residue was present. The residue was mixed with hot petroleum ether and then refrigerated at -5°C. The resulting crystals were

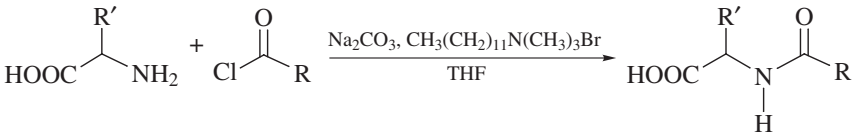
separated by filtration, resulting in a pure *N*-acylamino acid product in more than 90% yield.

CONCLUSION

We have demonstrated that the majority of *N*-acylamino acid derivatives can be prepared directly from the amino acid and acyl chlorides in one-pot syntheses. The procedure is exceptionally simple and a large quantity of desirable product can be obtained in this way. The procedure combines simple mixing of reactants and the catalyst in tetrahydrofuran as a solvent, stirring which then results in a suspension at room temperature, and finally refluxing for 5–8 h. The isolation of the product can be obtained by filtration, evaporation of the filtrate, and crystallization of residue after evaporation of tetrahydrofuran. This method has many advantages over the traditional ways of preparing these derivatives, which include protection, deprotection, and activation procedures, Due to its simplicity, it very easy to carry out and it is also very inexpensive. Therefore, it can be applied to large-scale industrial type *N*-acylamino acid preparation.

EXPERIMENTAL

All reagents are purchased from Aldrich and were used without further purification. The melting points were determined on an Electrothermal IA 9000 Digital Melting Point Apparatus. Mass spectroscopy was performed on a Micromass Quattro 2 Triple Quadrapole Mess Spectrometer. Elementary analysis was performed by Atlantic Microlab, Inc., Norcross, GA. The ^{1}H and ^{13}C-NMR spectra were recorded on a Varian Gemini NMR spectrophotometer (300 MHz) with DMSO-d_6 as a solvent. All signals ^{1}H and ^{13}C-NMR are referred to TMS as a standard. The IR spectra were recorded as KBr pellets on Nicolet 550 Magna Spectrophotometer. Thin layer chromatography (TLC) was performed on 0.2 mm silica gel 60 F_{254} with plastic support from Aldrich.



R′ = H,CH_3,$CH_3SCH_2CH_2$,$PhCH_2$,$CH_2CH(CH_3)_2$,$CH(CH_3)CH_2CH_3$
and as amino acid $H_2N(CH_2)_5COOH$ and $H_2NCH_2CONHCH_2COOH$
R = Ph, *p*-O_2NPh, *p*-O_2NPhO

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General Procedure for the Preparation of *N*-acylamino Acid Derivatives

A tetrahydrofuran (200 mL) suspension of sodium carbonate (3.5 g, 33 mmol), dodecyltrimethylammonium bromide (0.1 g, 0.33 mmol), the corresponding amino acid (33 mmol), and the corresponding acyl chloride (33 mmol) was stirred at room temperature for approximately 4 h. Then the reaction mixture was refluxed overnight (approximately 8–10 h) and the solid residue was separated from the tetrahydrofuran suspension and discarded. Tetrahydrofuran was evaporated, yielding a solid residue, which was then purified by crystallization.

Preparation of *N*-*p*-nitrobenzoylglycine

The white crystals left after evaporation of tetrahydrofuran were washed with petroleum ether and dried at 90°C for 5 h, yielding a pure product. The resulting yield was 89%. The melting point was determined to be 190°–192°C; IR 3450,3150,2950,2900,1750,1550, and a broad signal 3400–2400 cm^{-1}; ^{1}H-NMR; (DMSO-d_6), δ 9.18 (1H, t, NH), 8.32 (2H, d, Ar), 8.09 (2H, d, Ar), and 3.97 (2H, d, CH_2); ^{13}C-NMR (DMSO-d_6), δ 167, 161, 136, 125, 120, and 38; m/z 167(11%, $O_2NC_6H_4CONH^+$), 207(22%, $O_2NC_6H_4CONHCH_2CO^+$), 225(100%, $O_2NC_6H_4CONHCH_2COOH^+$).

Preparation of *N*-*p*-nitrobenzoylmethionine

The crystals remaining after tetrahydrofuran evaporation were washed with petroleum ether and dried at 90°C for 5 h, which yielded a pure product. The resulting yield was 90%. The melting point of this compound was determined to be 170°–171°C. IR 3300, 2900, 1730, 1650, 1600, 1530, 1350, and a broad signal at 3200–2400 cm^{-1}; ^{1}H-NMR (DMSO-d_6), δ 8.99 (1H, d, NH), 8.32 (2H, d, Ar), 8.15 (2H, d, Ar), 4.38 (1H, m. CH), 2.52 (2H, t, CH_2), 2.06 (2H, t, CH_2), and 2.02 (3H, s, CH_3); ^{13}C-NMR (DMSO-d_6), δ 169, 161, 135, 125, 119, 48, 36, 26, and 10; m/z 57(43%, H_2NCHCO^+), 75(9%, $H_3CSCH_2CH_2{}^+$), 120(100%, $C_6H_5CONH^+$), 168(12%, $O_2NC_6H_4CONH^+$), 251(43%, $O_2NC_6H_4CONHCH(COOH)CH_2CH_2^+$), 299(30%, $O_2NC_6H_4CONHCH(COOH)CH_2CH_2SCH_3{}^+$).

Preparation of *N*-benzoylglycine

After evaporation of tetrahydrofuran, the solid residue was slurred in petroleum ether and filtered. The white crystals were washed several times with small portions of petroleum ether (3 × 20 mL) and dried at 90°C. The resulting yield

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was 90%. The melting point was determined to be 188°–191°C. IR 3900, 2800, 3700, 3650, 3600, 3350, 2900, 2800, 1950, 1900, 1850, 1800, 1750, 1700, 1650, and a broad signal at 4000–2700 cm^{-1}; ^{1}H-NMR (DMSO-d_6), δ 8.86 (1H, t, NH), 7.84 (2H, d, Ar), 7.51 (2H, t, Ar), and 3.91 (1H, d, CH_2);^{13}C-NMR (DMSO-d_6), δ167, 162, 129, 127, 124, 123, and 36.

Preparation of *N*-*p*-nitrophenyloxycarbonylglycine

An oily residue after evaporation of tetrahydrofuran crystallized by staying at room temperature. ^{1}H-NMR spectrum showed about 80% of the product and about 15% *p*-nitrophenol. The crystals were slurred in 500 mL of benzene and the mixture was refluxed for 10 min. The insoluble solid was separated from the liquid and, standing at room temperature, white crystals were formed in the benzene filtrate. They were washed with petroleum ether. The melting point was determined to be ∼270°C with decomposition. IR 3400, 3100, 3000, 1730, 1550, 1250, and a broad signal at 3400–2600 cm^{-1}; ^{1}H-NMR (DMSO-d_6), δ 8.374 (1H, t, NH), 8.249 (2H, d, Ar), 7.04 (2H, d, Ar), and 3.80 (2H, d, CH_2); ^{13}C-NMR (DMSO-d_6) δ 172, 157, 154, 145, 126, 123, and 44; m/e 90 (7%, $HOOCNHCH_2^+$), 115(18%, $HOOCNHCH_2CO^+$), 140(100%, $O_2NC_6H_4O^+$), 169(7%, $HO_2NC_6H_4CHO)OH^+$), 241(10%, $O_2NC_6H_4OCONHCH_2COOH)$.$^+$ Anal. calcd for $C_9H_8N_2O_6$: C, 45.01; H, 3.36; N, 11.66. Found: C, 44.94; H, 3.43; N, 11.53.

Preparation of *N*-benzoylmethionine

After evaporation of tetrahydrofuran, white crystals were slurred in petroleum ether (100 mL), separated by filtration, and washed with petroleum ether (3 × 20 mL). The yield of *N*-benzoylmethionine is 92%. The melting point was determined to be 176°–177°C. IR 3900, 3800, 3700, 3650, 3600, 3300, 3000, 2900, 1950, 1900, 1850, 1600, and a broad signal at 4000–2700 cm^{-1}; ^{1}H-NMR (DMSO-d_6) δ 8.48 (1H, d, NH), 7.80 (2H, d, Ar), 7.45 (1H, t, Ar), 7.35 (2H, t, Ar), 4.40 (1H, m, CH), 2.50 (2H, m, CH), 2.00 (2H, t, CH_2), 1.90 (1H, s, CH_3); ^{13}CNMR (DMSO-d_6), δ 169, 162, 129, 127, 124, 123, 60, 47, 26, and 10; m/e 61(20%, $^+H_2CSCH_3$), 105(76%, $C_6H_5CO^+$), 206(47%, $C_6H_5CONHCH(CH_2CH_2^+)COOH$), 236(25%, $C_6H_5CONHCH(CH_2CH_2SCH_3)CO^+$), 254(100%, $C_6H_5CONHCH(CH_2CH_2SCH_3)COOH)^+$. Anal. calcd for $C_{12}H_{15}NO_3S$: C, 56.90; H, 5.97; N, 5.53; S, 12.66. Found: C, 56.81; H, 6.02; N, 5.48; S, 12.58.

Preparation of *N*-benzoylalanine

Tetrahydrofuran was evaporated and the solid residue was slurred in petroleum ether (100 mL) and separated by filtration. White crystals were washed

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with petroleum ether (3 × 20 mL), yielding pure *N*-benzoylalanine. The resulting yield was 93%. IR 3300, 3100, 2900, 1730, and a broad signal at 3400–2200 cm^{-1}. ^{1}H-NMR (DMSO-d_6), δ 8.58(1H, t, NH), 7.92(2H, d, Ar), 7.56(3H, t, Ar), 3.45(1H, dq, CH), and 2.58(3H, d, CH_3). ^{13}C-NMR (DMSO-d_6), δ 173, 166, 134, 131, 128, 127, 36, and 34; m/z 176 ($C_6H_5CONHCH(CO^+)CH_3$), 194 ($C_6H_5CONHCHCH(COOH)CH_3^+$). Anal. calcd for $C_{10}H_{12}NO_3$: C, 61.85; H, 6.23; N, 7.21. Found: C, 61.75; H, 6.29; N, 7.16.

Preparation of *N*-benzoylphenylalanine

After evaporation of tetrahydrofuran, the resulting oil was crystallized in an ice bath. The crystals were filtered and washed with petroleum ether (3 × 20 mL), and the filtrate was discarded. The resulting yield was 91%. The melting point was determined to be 184°–185°C. IR 3500, 3100, 2950, 2750, 2650, 1750, and a broad signal at 3400–2200 cm^{-1}; ^{1}H-NMR (DMSO-d_6), δ 8.58, 7.90, 7.46, 7.42, 4.41, 1.71, 1.57, and 0.9; ^{13}C-NMR (DMSO-d_6), δ 170, 162, 129, 127, 124, 123, 46, 20, 18, and 17; m/z 57(100%, $^{+}H_2CCH(CH_3)_2$), 105(53%, $C_6H_5CO^+$), 190(43%, $C_6H_5CONHCH^+CH_2CH(CH_3)_2$), 218(65%, $C_6H_5CONHCH(CO^+)CH_2CH(CH_3)_2$), 236(80%, $C_6H_5CONHCH(CH_2CH(CH_3)_2COOH$).

Preparation of *N*-benzoylisoleucine

After evaporation of tetrahydrofuran, the oily residue was crystallized in an ice bath. The crystals were slurred in petroleum ether (100 mL) and washed with petroleum ether (3 × 20 mL). The yield was 91%. The melting point was determined to be 135°–136°C. IR 3300, 2950, 2900, 2800, 1730, and a broad signal at 3300–2600 cm^{-1}; ^{1}H-NMR (DMSO-d_6), δ 8.29, 7.84, 7.50, 7.43, 4.30, and 0.8; ^{13}C-NMR (DMSO-d_6), δ 169, 162, 130, 127, 123, 123, 52, 32, 21, 11, and 7; m/z 57(100%, $^{+}H_2CCH(CH_3)_2$), 105(23%, $C_6H_5CO^+$), 190(27%, ($C_6H_5CONHCH^+(CH_2CH(CH_3)_2$), 218(33%, $C_6H_5CONHCHCO^+$ ($CH_2CH(CH_3)_2^+$), 236(25%, $C_6H_5CONHCHCO(CH_2CH(CH_3)_2)COOH^+$). Anal. calcd for $C_{13}H_{17}NO_3$: C, 66.36; H, 7.28; N, 5.95. Found: C, 66.31; H, 7.33; N, 5.88.

Preparation of *N*-benzoyl-6-aminohexanoic Acid

After evaporation of tetrahydrofuran, the white crystals were washed with petroleum ether (3 × 20 mL), yielding pure *N*-benzoyl-6-hexanoic acid. The resulting yield was 88%. IR 3900, 3800, 3700, 3650, 3600, 3300, 2900, 2800, 2700, 1950, 1900, 1850, 1800, 1700, and a broad signal at 4000–2700 cm^{-1}; ^{1}H- NMR

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(DMSO-d_6), δ 8.50 (1H, t, NH), 7.83 (2H, d, Ar), 7.55 (1H, t, Ar), 7.46 (2H, t, Ar), 3.24 (2H, q, CH_2), 2.20 (2H, t, CH_2), 1.52 (4H, m, CH_2), and 1.30 (2H, m, CH_2). ^{13}C-NMR (DMSO-d_6), δ 170, 161, 130, 127, 124, 123, 35, 29, 24, 22, and 20; m/z 57(100%, $^+CH_2CH_2CH_2CH_3$, 105(60%, $C_6H_5CO^+$), 117(25%, $^+(CH_2)_5COOH$), 218(27%, $C_6H_5CONH(CH_2)_5CO^+$), 236(34%, $C_6H_5CONH(CH_2)_5COOH^+$). Anal. calcd for $C_{13}H_{17}NO_3$: C, 66.36; H, 7.28; N, 5.95. Found: C, 66.26; H, 7.37; N, 5.90.

Preparation of *N*-(*N′*-benzoyl-2-aminoethanoyl)-2-aminoethanoic Acid

The resulting suspension was filtered while tetrahydrofuran was still hot, and the filtrate was discarded. The remaining crystals were dissolved in 50 mL of water at elevated temperature, and then acidified with HCl (20 mL) until the pH reached around 2.00. The formed white crystals were separated by filtration and dried at 60°C. The yield was 92%. IR 3350, 3100, 2970, 1730, 1250, and a broad signal at 3400–2200 cm^{-1}; ^{1}H-NMR (DMSO-d_6), δ 8.83(1H, d, NH), 8.45(1H, t, NH), 7.90(2H, d, Ar), 7.57(1H, t, Ar), 7.46(2H, t, Ar), 3.92(2H, d, CH_2), and 3.74(2H, d, CH_2); ^{13}C-NMR (DMSO-d_6), δ 172, 169, 167, 134, 132, 128, 127, 43, and 41; m/z 105(10%, $C_6H_5CO^+$), 120(15%, $C_6H_5CONH^+$), 134(10%, $C_6H_5CONHCH_2^+$), 162 (100%, $C_6H_5CONHCH_2CO^+$), 219(20%, $C_6H_5CONHCH_2CONHCH_2CO^+$), 237(45%, $C_6H_5CONHCH_2CONHCH_2COOH^+$).

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