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Diacetamides. II.*

Syntheses and Properties of Some *N,N*-Diacylamino Esters

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By using the ^{14}C -tracer technique it was established that the carbon dioxide evolved in the reaction of β -ureido ester I with acetic anhydride originates from the carbonyl of the ureido group. *N,N*-Diacylamino esters and *N*-acylamino esters were also obtained from α -ureido ester II and acetic anhydride, as well as from propionic acid anhydride and β -ureido ester I. In addition *N,N*-dipropionylamino ester VII and *N*-propionylamino ester VIII were synthesized from the corresponding β -amino ester and *N*-carbonyl ester, respectively. It was shown that the conversion of *N,N*-diacylamino esters into the monoacylamino esters occurs readily if small amounts of acetic and propionic acid, respectively, were present in the boiling anhydride. Reduction of *N,N*-diacetylamino ester II with lithium aluminium hydride gave the dialkylamino alcohol XII.

It has been shown¹, that β -ureido esters when refluxed with acetic anhydride undergo fission with the evolution of carbon dioxide and the formation of the corresponding diacetamides. As an intermediate in this reaction a mixed carbaminic-carboxylic anhydride^{2,3} was presumed. Isocyanates, which would be expected as intermediate products were detectable in very small amounts only at the beginning of the reaction.

In this work we tried to get a better insight into the mechanism and the general applicability of this reaction, as well as to get more knowledge about the chemical and physical properties of the obtained diacylamino esters.

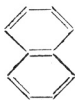
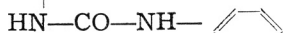
In order to establish the origin of the carbon dioxide evolved in the reaction of the anhydride with β -ureido esters, ethyl β -naphthylureido-butyrates I, labeled with ^{14}C in the ureido group⁴ was refluxed with acetic anhydride. Carbon dioxide was the only radioactive product (Table I). This fact confirms that in this type of reaction the total amount of the evolved carbon dioxide originates from the carbonyl of the ureido group. It is likely that it was generated by decomposition of the intermediate carbaminic-carboxylic anhydride.

Thus, it could be assumed that the action of acetic anhydride on ureido ester (A) proceeds through the acetylated product (B), which then, under simultaneous attack of the acylium and acetate ions, undergoes fission into a mixed anhydride (C) and a monoacetylated amine (D). The unstable carbaminic-

* Paper I, A. Kornhauser and D. Keglević, *Tetrahedron* 18 (1962) 7.

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β -amino esters and β -*N*-carbonyl esters, these compounds were also subjected to the reaction with propionic anhydride.

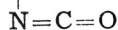


I $n = 1$

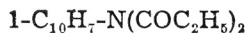
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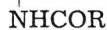
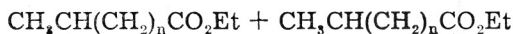
V



VI



IX



III $n=0$, $\text{R}=\text{CH}_3$

IV $n=0$, $\text{R}=\text{CH}_3$

VII $n=1$, $\text{R}=\text{C}_2\text{H}_5$

VIII $n=1$, $\text{R}=\text{C}_2\text{H}_5$

X $n=1$, $\text{R}=\text{CH}_3$

XI $n=1$, $\text{R}=\text{CH}_3$

When the ureido ester I, ethyl β -aminobutyrate (V) and ethyl β -*N*-carbonyl-butyrate (VI) respectively were refluxed in propionic anhydride, the qualitative picture of the reaction was the same as with acetic anhydride. Ethyl *N,N*-dipropionyl- β -aminobutyrate (VII) and ethyl *N*-propionyl- β -aminobutyrate (VIII) were isolated as the reaction products in all three cases. However, the yields of VII were rather poor, although the ureido ester I as well as the *N*-carbonyl ester VI evolved an almost quantitative amount of carbon dioxide during the first hour of refluxing. When the same reactions were performed at 140° , the yields on VII improved considerably. (Table II). However, in no case they were as high as with the corresponding diacetyl amino derivative.

As expected from the analogy with the acetyl amino derivatives, the *N*-carbonyl ester VI gave VII in the highest yield. The separation of dipropionyl-amino derivative VII from monopropionyl amino derivative VIII was performed on a charcoal — celite column as already described¹. In the case of the ureido ester I, the separation of VII and VIII from *N,N*-dipropionyl-1-naphthylamine (IX) proved to be a tedious process, because of the low melting point and sluggishness of crystallization of IX. It is interesting that the yield of IX remained unchanged whether the reaction was performed at 160° or at 140° . β -Amino ester V gave the lowest yield of VII in spite of the fact that the time of the reaction was extended.

TABLE II

Yields of *N,N*-Dipropionyl- β -aminoester VII and *N*-Propionyl- β -aminoester VIII

Starting compound	Reaction at 166°		Reaction at 140°	
	%		%	
	VII	VIII	VII	VIII
Ureido ester I	12.4	53.0	28.0	45.0
Amino ester V	7.6	49.5	20.2	41.2
<i>N</i> -Carbonyl ester VI	21.0	45.0	45.7	37.4

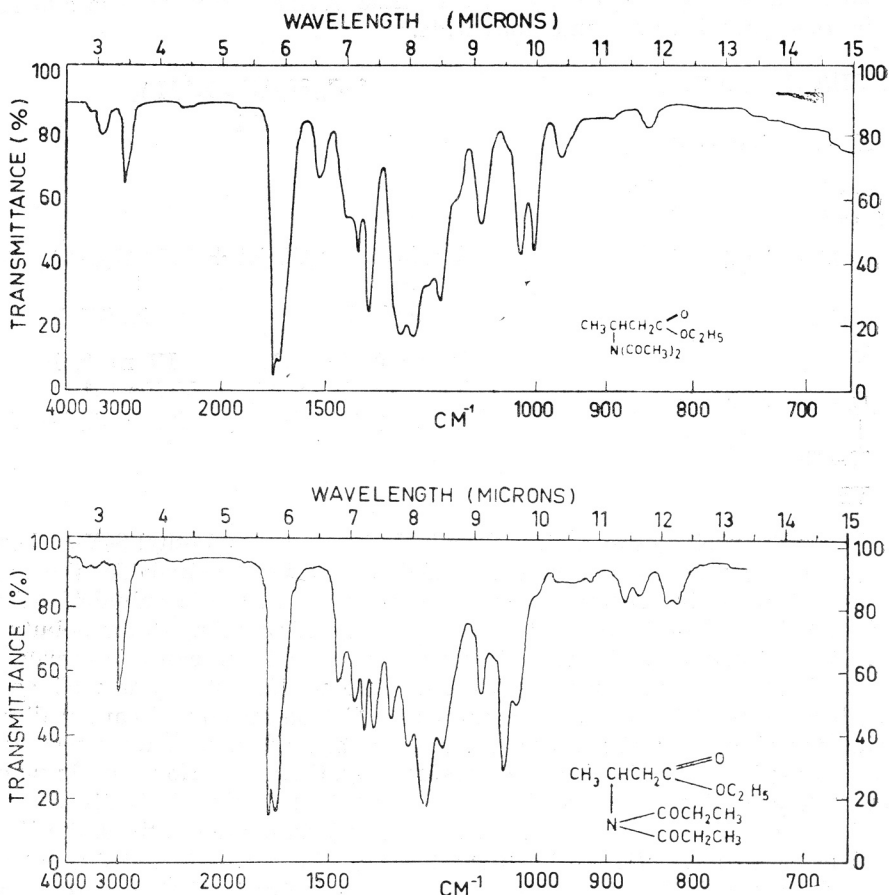


Fig. 1. IR spectra of *N,N*-dipropionylamino ester VII and *N,N*-diacetyl-amino ester X.

These results indicate that the reaction of ureido esters with acid anhydrides is a general one.

The comparison of the IR spectra of *N,N*-dipropionylamino ester VII with the corresponding *N,N*-diacetyl-amino ester X, shows (Fig. 1.) that the characteristic absorptions fall in the same region (diamido carbonyls⁶ at 5.70 μ and 5.90 μ). The lacking of the N-H bands⁷ at 3 μ and 6.45 μ is indicative that no monoacylamino derivative was present.

In the literature^{8,9} some diacetyl-amino compounds are referred as acetylating agents. We tried this reaction with ethyl diacetyl-amino-butyrates X and aniline in benzene; acetanilide was isolated in 56% yield.

To obtain some more information about the stability of the *N,N*-diacetyl-amino esters, we refluxed the diacetyl-amino ester X with glacial acetic acid. In one hour X was converted completely into ethyl *N*-acetyl- β -aminobutyrate (XI). The same reaction took place partially also with the anhydrides containing small quantities of the acid. Therefore, the content of the acid in the anhydride

was determined¹⁰. It was found that the conversion of X to XI was proportional with the amount of the remaining acid present in the commercial and purified anhydride.

For further characterisation, the *N,N*-diacetyl-amino ester X was reduced with lithium aluminium hydride; *N,N*-diethyl-3-aminobutanol-1 (XII) was obtained in 53% yield. This way seems to be a convenient route for the preparation of *N,N*-dialkyl-aminoalcohols.

EXPERIMENTAL

All melting points are uncorrected.

Material and Methods

1. *Anhydrides*. Acetic anhydride (BDH, Analar) was purified through a Siegwarth column as described earlier¹. Propionic anhydride (Fluka, *puriss.*) was distilled over a 50 cm. column, the fraction b. p. 166—168° being collected. If not stated otherwise, these anhydrides were used throughout the work.

The purity of commercial and rectified anhydride was determined by the morpholine method¹⁰ which measures the anhydride independent of the acid content of the sample.

Anal. Anhydride found: Acetic anhydride, BDH, Analar: 95.64%; the same, purified: 98.21%. Propionic anhydride, Fluka, *puriss.*: 90.53%; the same, purified: 98.19%.

2. *Determination of carbon dioxide*. In inactive experiments CO₂ was determined quantitatively as already described¹. In the ¹⁴C-experiment, a 100 ml. two-necked flask was equipped with a gas inlet tube and a condenser which was connected through a trap cooled with a dry ice-acetone mixture with two alternatively connected 250 ml. washing bottles. Dry nitrogen was bubbled through the system during the reaction. The evolved CO₂ was absorbed at suitable intervals, without interruption, in 0.5 N carbonate-free sodium hydroxide and converted into BaCO₃ samples by standard procedure¹¹.

3. *Determination of radioactivity*. The labelled ureido ester I-¹⁴C was burned in a dry-combustion micro-apparatus¹² and converted into BaCO₃¹¹. The radioactivity was measured on samples of »infinite thickness« in a gas flow counter (Tracerlab).

4. *Chromatography on carbon-celite columns*. The chromatography was carried on a 2:1 mixture of deactivated carbon and celite (BDH). The diacetyl-amino derivatives were eluted with petroleum ether — chloroform and the monoacetyl-amino derivatives with chloroform as already described¹.

Ethyl α-[(1'-naphthyl)-ureido]-propionate (II)

II was prepared according to Morsch¹³ and Schlögl¹⁴ from 3.05 g. (24.0 mmoles) ethyl D,L-alaninate and 4.06 g. (24.0 mmoles) 1-naphthylisocyanate in anhydrous ether. Yield: 5.20 g., 75.5%. After two recrystallizations from chloroform — petroleum ether, the substance was analytically pure, m. p. 135—137°.

Anal. C₁₆H₁₈N₂O₃ (286.32) calc'd.: C 67.11; H 6.34; N 9.78%
found: C 67.15; H 6.67; N 10.01%

Ethyl *N,N*-diacetyl-α-aminopropionate (III) and Ethyl *N*-acetyl-α-aminopropionate (IV)

II (5.0014 g., 17.45 mmoles) was refluxed with 30 ml. of acetic anhydride for 5 hours. The evolved carbon dioxide was measured quantitatively; 60.1% of the theoretical amount was collected. After evaporation of the anhydride, the residue was dissolved in chloroform, petroleum ether added and after standing overnight at 0°, the *N,N*-diacetyl-1-naphthylamine (2.8437 g.; 71.9%), m. p. 126—128°¹⁵ collected. The solvent was evaporated *in vacuo*, the remaining oil distilled (b. p. 80—90°/0.015 mm.), and subjected to charcoal-celite chromatography¹. Petroleum ether — chloroform eluates afforded 1.0134 g. (28.8%) of III, and chloroform eluates gave 0.581 g. (20.8%) of IV.

For analysis III was distilled at 80—82°/0.015 mm, as a colourless oil.

Anal. C₉H₁₅NO₄ (201.22) calc'd.: C 53.72; H 7.51; N 6.96%
 found: C 53.51; H 7.46; N 7.04%
 calc'd.: acetyl* 42.60%
 found: acetyl 42.32%

IV (b. p. 100—102°/0.2 mm.) proved to be identical with the already described⁵ ethyl *N*-acetylalaninate:

Anal. C₇H₁₃NO₃ (159.18) calc'd.: C 52.82; H 8.23; N 8.80%
 found: C 52.55; H 8.54; N 9.00%
 calc'd.: acetyl 27.04%
 found: acetyl 26.97%

Preparation of Ethyl N,N-dipropionyl-β-aminobutyrate (VII) and Ethyl N-propionyl-β-aminobutyrate (VIII)

1. From ethyl β-[3-(-1'-naphthyl)-ureido]-butyrate (I)

a) at 166°. I (2.5755 g., 8.57 mmoles) and 17 ml. of propionic anhydride were refluxed for 2 hours. Already after one hour 96% of the theoretical amount of CO₂ was evolved. After the removal of the anhydride, the viscous oil was triturated with 5 ml. of ligroin and left at 0° for 48 hours. Crystals of *N,N*-dipropionyl-1-naphthylamine (IX) were filtered off and washed with ligroin; yield 1.0500 g., 48.0%, m. p. 61—66°. For analysis, the sample was recrystallized twice from ligroin, m. p. 68.5—70°.

Anal. C₁₆H₁₇NO₂ (255.31) calc'd.: C 75.26; H 6.71; N 5.49%
 found: C 75.35; H 7.00; N 5.75%

The mother liquor was evaporated *in vacuo*, the remaining oil distilled (94—98°/0.02 mm.) and subjected to charcoal — celite chromatography. The yields of isolated VII and VIII are given in Table II.

VII: colourless oil, b. p. 92—95°/0.02 mm.

Anal. C₁₂H₂₁NO₄ (243.30) calc'd.: C 59.24; H 8.70; N 5.76%
 found: C 59.17; H 8.55; N 6.08%

VIII: colourless oil, b. p. 98—100°/0.02 mm.

Anal. C₉H₁₇NO₃ (187.24) calc'd.: C 57.73; H 9.15; N 7.48%
 found: C 57.60; H 9.29; N 7.66%

b) at 140°. I (2.4380 g., 8.12 mmoles) and propionic anhydride (15 ml.) were kept at 140—145° for 3 hours. The quantity of CO₂ was measured each hour and was found to be: 45.0, 30.4, and 19.3% resp.; total: 95.2%. The reaction mixture was worked out as described under *a*. 947.4 mg. (45.6%) of dipropionylamino naphthalene IX was obtained. The yields of VII and VIII are given in Table II.

2. From ethyl β-aminobutyrate (V)

a) at 166°. Amino ester V (2.0150 g., 15.41 mmoles) was refluxed with 15 ml. of propionic anhydride for 5 hours. After the removal of the anhydride, the obtained oil was distilled (98—105°/0.03 mm.) and subjected to charcoal — celite chromatography.

b) at 140°. 2.8706 g. (21.9 mmoles) V and 12 ml. of propionic anhydride were heated at 140—145° for 12 hours. The yields of VII and VIII are presented in Table II.

3. From ethyl β-*N*-carbonyl butyrate (VI)

a) at 166°. 2.4673 g. (15.62 mmoles) VI and 13 ml. of propionic anhydride were refluxed for 90 minutes. The amounts of the evolved CO₂ were 87.4% after 45 min., and 5.0% after further 45 min. The anhydride was removed *in vacuo*, the residue distilled and subjected to column chromatography.

b) at 140°. 1.8758 g. (11.92 mmoles) VI and 12 ml. of propionic anhydride were kept at 140—145° for 4 hours. The evolved CO₂ was measured in one-hour intervals

* Kuhn-Roth micro-acetyl, alkaline saponification.

and was found to be: 44.0, 23.6, 6.4, and 3.4% resp.; total: 77.4% of the theoretical amount. Yields of VII and VIII are given in Table II.

The identity of VII and VIII prepared under 1., 2., and 3. was established by elemental and acetyl analysis and by IR spectra.

Reaction of Ethyl N,N-diacetyl-β-aminobutyrate (X) with:*

1. *aniline*. X (1.2942 g., 6.02 mmoles) and aniline (560 mg., 6.04 mmoles) were refluxed with 10 ml. of benzene for 4 hours. After evaporation of the solvent, the remaining oil was poured into water, and the obtained solid recrystallized from water. Crystals, 455 mg., (56.0%), m. p. 111—113° gave no depression with an authentic sample of acetanilide.

2. *acetic acid*. X (1.5947 g., 7.42 mmoles) was refluxed with 6 ml. of glacial acetic acid for one hour. After removing the acid, the remaining oil was distilled (b. p. 96—102°/0.02 mm.), and identified by elemental analysis and IR spectra as ethyl N-acetyl-β-aminobutyrate (XI). Yield: 1.0288 g., 80.0%.

3. *acetic anhydride*. X (611 mg., 2.84 mmoles) was refluxed with 5 ml. of acetic anhydride (BDH, Analar) for 3 hours. After evaporation of the anhydride, the oil was distilled and subjected to column chromatography. 390 mg. (63.7%) of unchanged X and 131 mg. (26.6%) of the corresponding monoacetyl amino ester XI were obtained.

When X was refluxed with the purified anhydride for 3 hours, and the mixture worked up in the same manner, 82.3% of unchanged X and 11.0% of XI were obtained.

Reaction of N,N-dipropionylamino ester VII with propionic anhydride

Analytically pure VII (814 mg., 3.34 mmoles) and 10 ml. of propionic anhydride (Fluka, *puriss.*) were refluxed for 90 minutes. After column chromatography, 473.8 mg. (58.2%) of unchanged VII and 202 mg. (32.2%) of the corresponding monopropionylamino ester VIII were isolated.

When the same process was performed under identical conditions with the purified anhydride, 70.2% of VII and 15.1% of VIII were isolated.

N,N-Diethyl-3-aminobutanol-1 (XII)

Diacetyl amino-butyrate X (949 mg., 4.4 mmoles) was dissolved in 20 ml. of anhydrous ether and added dropwise at 0° into a stirred suspension of LiAlH₄ (379 mg., 10 mmoles) in anhydrous ether (30 ml.). The stirring was continued at room temperature for additional 2 hours. The complex was decomposed with ethanol (1 ml.) and water (0.5 ml.), the mixture filtered, dried over KOH and the solvent evaporated *in vacuo*. The residue was distilled and 345 mg. (53.5%) of XII, b. p. 85—90°/18 mm. as a liquid oil was obtained.

Anal. C₈H₁₉NO (145.24) calc'd.: N 9.64%
found: N 9.72%

Acknowledgment. The authors are indebted to Mrs. Đ. Orlić for valuable technical assistance.

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* In these experiments analytically pure X was used.

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IZVOD

Diacetamidi II. Sinteze i svojstva nekih *N,N*-diacilamino estera

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Primjenom markiranog ugljika dokazano je da ugljični dioksid, koji se razvija kod reakcije anhidrida octene kiseline sa β -ureido esterom, potječe isključivo iz ureido skupine. Iz etil α -ureidopropionata dobiveni su djelovanjem anhidrida octene odgovarajući *N,N*-diacil-, odnosno *N*-acil-amino esteri. Iz etil β -ureidobutirata I sa anhidridom propionske kiseline nastali su pak *N,N*-dipropionil-, odnosno *N*-propionil-aminobutirat. Ti rezultati ukazuju na općenitost reakcije ureido estera sa anhidridima. Kao polazne supstance za pripravu dipropionilamino estera VII i propionilamino estera VIII upotrebljen je i β -amino ester V, te *N*-karbonil ester VI. Ispitivano je ponašanje diacilamino estera u ledenoj octenoj kiselini, te anhidridima octene i propionske kiseline.

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