ON THE ACTION OF HYDRAZINE ON N-ACYL AND N-AMINOACYL DERIVATIVES OF DIKETOPIPERAZINES

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Abstract

Full Text

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ON THE ACTION OF HYDRAZINE ON N-ACYL AND N-AMINOACYL DERIVATIVES OF DIKETOPIPERAZINES

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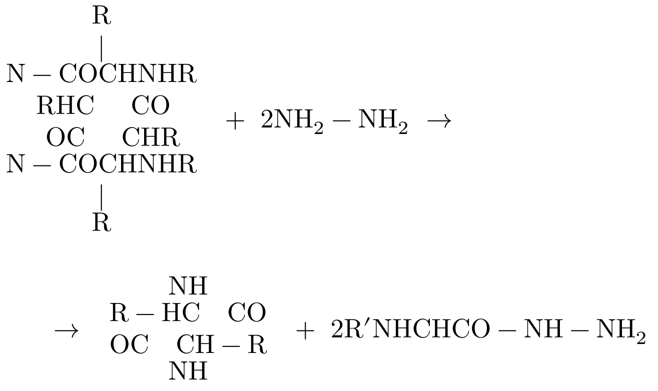
Earlier we (1) studied the action of hydrazine on N,N′-di-(phthalylglycyl)-diketopiperazine and showed the versatility of this action. It amounted 1) to addition of hydrazine at the –CO groups of the phthalyl protecting group when the reaction was carried out in ether or alcohol in the cold, 2) to cleavage of the phthalyl group on heating in alcohol, and 3) to cleavage of the diketopiperazine ring with formation of phthalyltripeptide hydrazide, without rupture of the acyl bond.

In the present work one more specific property of hydrazine has been found: it is, in a sense, an acceptor of acyl and N-aminoacyl groups of diketopiperazines. On interaction of hydrazine with both acylated and aminoacylated diketopiperazines, quantitative transacylation and transaminoacylation occur, accompanied by regeneration of the free diketopiperazine. This reaction proceeds almost instantaneously in the cold (1) upon addition of hydrazine to the corresponding diketopiperazine derivatives in alcohol, ether, or chloroform. Thus, hydrazine can serve as a distinctive reagent for the presence, in diketopiperazine derivatives, of N-acyl and N-aminoacyl forms of bonds.



$$\begin{array}{c} \mathrm{R} \\ | \\ \mathrm{N-COCHNHR} \\ \mathrm{RHC\quad CO} \\ \mathrm{OC\quad CHR} \\ \mathrm{N-COCHNHR} \\ | \\ \mathrm{R} \end{array} + 2\mathrm{NH_2-NH_2} \rightarrow \tag{1}$$

$$\rightarrow \begin{array}{c} \mathrm{NH} \\ \mathrm{R-HC\quad CO} \\ \mathrm{OC\quad CH-R} \\ \mathrm{NH} \end{array} + 2\mathrm{R'NHCHCO-NH-NH_2}$$

For the first time we find the use of hydrazine as a structural reagent in the work of Stoll and co-workers on establishing the structure of ergot alkaloids (2). The action of hydrazine on the molecule of these compounds led the investigators to establish both their diketopiperazine structure and the presence of the N-aminoacyl form of bonding. In 1956, Brockmann and co-workers (3), subjecting actinomycin to hydrazine cleavage, isolated D,L-N-methylvalylsarcosine hydrazide and prolylvaline hydrazide.

Experimental Part

1. Action of hydrazine on derivatives of phenylalanine anhydride:

a) Action on N,N′-diacetylphenylalanine anhydride. 0.5 g of diacetylphenylalanine anhydride was dissolved in 10 ml of chloroform. To the clear solution 0.2 ml of hydrazine hydrate was added. On standing, a precipitate formed; it was filtered off and washed with alcohol. According to its m.p. 301° and analysis, the isolated compound is phenylalanine anhydride.

Found, %:	C 73.35; 73.20;	H 6.26; 6.38;	N 9.71; 9.72 (Dumas)
$C_{18}H_{18}N_2O_2$. Calculated, %:	C 73.43;	H 6.17;	N 9.53

From the chloroform filtrate acetylhydrazide was isolated (4). M.p. 67°.

b) Action on N,N′-di-(phthalylglycyl)-phenylalanine anhydride. To 0.1 g of di-(phthalylglycyl)-phenylalanine anhydride, dissolved in 10 ml of chloroform, 0.1 ml of hydrazine was added. After an hour the precipitate that had formed was filtered off, washed with abs. ether, and dried in a vacuum desiccator. Weight 0.014 g. M.p. 301°. According to literature data (5), 301°. The precipitate is phenylalanine anhydride.

The phthalylglycylhydrazide isolated upon concentration of the chloroform filtrate was hydrolyzed with 10% HCl for 26 hours. On a paper chromatogram (solvent: butanol, water, acetic acid) only glycol was detected. Thus the reaction proceeds quantitatively according to (1).

Found, %:	N 23.98 (Dumas)
$C_{10}H_9O_3N_3$. Calculated, %:	N 24.13

c) Action on N,N′-di-(phthalylalanyl)-phenylalanine anhydride. To a solution of 0.1 g of di-(phthalylalanyl)-phenylalanine anhydride in 10 ml of chloroform, 0.1 ml of hydrazine was added. The precipitate that formed was washed with abs. ether to remove hydrazine. The precipitate was dried. Weight 0.013 g. M.p. 301°. The isolated substance is phenylalanine anhydride. In the compound obtained from the chloroform filtrate, one amino acid—alanine—was detected on a paper chromatogram after hydrolysis. Thus, the substance is phthalylalanylhydrazide.

Found, %:	N 17.91 (Dumas)
$C_{11}H_{11}O_3N_3$. Calculated, %:	N 18.02

the reaction proceeds according to (1).

d) Action on N,N′-di-(phthalylvalyl)-phenylalanine anhydride. To 0.5 g of di-(phthalylvalyl)-phenylalanine anhydride were added 5 ml of abs. alcohol and 0.12 g of hydrazine hydrate. After 5 min the initially clear solution becomes turbid. Precipitation of the solid is complete after 15 min. After standing for an hour at room temperature, the precipitate was filtered off and washed with alcohol. The m.p. of the substance is 301°. Yield 0.9 g, i.e., theoretical, calculated as phenylalanine anhydride.

From the alcoholic filtrate, upon concentration, phthalylvalylhydrazide was isolated.

Found, %:	N 15.89 (Dumas)
$C_{13}H_{15}O_3N_3$. Calculated, %:	N 16.07

A paper chromatogram after hydrolysis of this compound indicated the presence in it of one amino acid—valine.

e) Action on N,N′-di-(phthalylleucyl)-phenylalanine anhydride. To 0.5 g of N,N′-di-(phthalylleucyl)-phenylalanine anhydride, dissolved in 10 ml of abs. chloroform, 0.12 g of hydrazine hydrate was added. After 5 min the initially completely clear solution rapidly crystallized. After 10 min the precipitate was filtered off and washed with alcohol to remove hydrazine hydrate. M.p. 300-301°. Yield—quantitative,

calculated as phenylalanine anhydride. Paper chromatographic analysis of the acid hydrolysate of the substance isolated from the alcohol filtrate revealed only leucine.

$C_{14}H_{17}O_3N_3$.	Found, %:	N 15.31 (Dumas)
	Calculated, %:	N 15.26

2. Action of hydrazine on glycine anhydride derivatives:
a) Action on N,N′-diacetylglycine anhydride in absolute ethyl alcohol. To 1.0 g of diacetyldiketopiperazine [6] in 15 ml of alcohol (dissolution on heating), 0.39 g of hydrazine was added. The reaction is accompanied by strong heating and quantitative precipitation of diketopiperazine (0.5 g). M.p. 316°. From the alcoholic filtrate, on concentration, acetylhydrazide was isolated. M.p. 66-67°. According to the literature, 67° [4].

b) Action on N,N′-diacetylglycine anhydride in absolute ether. To 1.0 g of diacetyldiketopiperazine in 30 ml of absolute ether, 0.39 g of hydrazine was added with strong cooling and shaking. On standing for 30 min, a precipitate separated, which was filtered off and washed with ether. M.p. 316°.

$C_4H_6O_2N_2$.	Found, %:	N 24.37 (Kjeldahl)
	Calculated, %:	N 24.56%

Yield—0.5 g, i.e., theoretical, calculated as diketopiperazine. From the ether filtrate acetylhydrazide was isolated. M.p. 67°. According to the literature, 67° [4].

c) Action on N-acetylglycine anhydride in alcohol. 0.5 g of monoacetyldiketopiperazine [7] was dissolved in 20 ml of alcohol on heating. To the cooled solution, 0.2 g of hydrazine was added. Immediate precipitation of a solid was observed; it was filtered off and washed with alcohol. By m.p. 316° and by its properties it is diketopiperazine. Acetylhydrazide [4] was isolated from the filtrate.

d) Action on N,N′-di-(phthalylleucyl)-glycine anhydride. 0.5 g of N,N′-di-(phthalylleucyl)-glycine anhydride and 1.6 ml of a 1 M alcoholic solution of hydrazine hydrate were heated in 6 ml of absolute alcohol for one hour. The solution was cooled at room temperature, the precipitate was filtered off, washed with alcohol, and recrystallized from 50% hot alcohol. By paper chromatographic analysis after hydrolysis, the substance was identified as phthalylleucylhydrazide.

$C_{14}H_{17}O_3N_3$.	Found, %:	N 15.19 (Dumas)
	Calculated, %:	N 15.26

The portion of the precipitate that did not dissolve on treatment with alcohol, according to m.p. 316° and its properties, is diketopiperazine.

e) Action on N,N′-di-(phthalylalanyl)-glycine anhydride. The reaction with hydrazine was carried out as described for N,N′-di-(phthalylleucyl)-glycine anhydride. Diketopiperazine was isolated, and from the filtrate phthalylalanylhydrazide. The latter compound was characterized by a paper chromatogram of its hydrolysate and by identity with phthalylalanylhydrazide isolated from reaction 1c. A mixed-melting test of these hydrazides gave no depression.

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CITED LITERATURE

1. L. N. Akimova, N. I. Gavrilov, ZhOKh, **23**, 335 (1953).

2. A. Stoll, Th. Petrzilka, B. Becker, Helv. Chim. Acta, **33**, 57 (1950).

3. H. Brockmann, G. Bohnsack, C. H. Süling, Angew. Chem., **68**, No. 2, 66 (1956).

4. R. Stollé, J. prakt. Chem., (2), **69**, 145 (1904).

5. E. Fischer, Ber., **10**, 1967 (1888); **34**, 435 (1901).

6. A. P. N. Francimont, H. Friedman, Rec. trav. chim., **27**, 192 (1908).

7. R. G. Petrova, L. N. Akimova, N. I. Gavrilov, ZhOKh, **24**, 2230 (1954).

Note: Figure translations are in progress. See original paper for figures.