Chemistry of Heterocyclic Compounds, Vol. 34, No. 10, 1998

CYCLIZATION OF N-DIACETIC AMINO ACIDS

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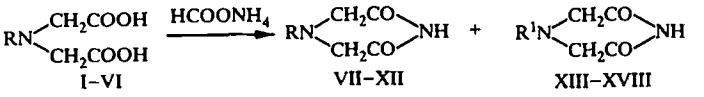
Cyclization of a number of N-diacetic amino acids has been carried out. The dependence of the cyclization products — 3,5-dioxopiperazinoalkanecarboxylic acids and/or their amides - on the temperature, ratio of components, and the presence of solvent has been established.

3,5-Dioxo-1-piperazinoacetamide was obtained in 46% yield on heating nitrilotriacetic acid in excess formamide [1]. There is no other information on the synthesis of piperazinedione-2,6 containing amino acid residues. We recently described a method for preparing piperazinedione-2,6 [2]. In the present work we first used ammonium formate for the cyclization of N-diacetic acids, derivatives of the corresponding amino acids. The starting materials used were N-diacetic acids: nitrilotriacetic (I), α-alanine-N-diacetic (II), β-phenyl-α-alanine-N-diacetic (III), β-phenyl-β-alanine-N-diacetic (IV) [3] and 4-(N,N-dicarboxymethylamino)butanoic (V) and 7-(N,N-dicarboxymethylamino)heptanoic (VI) acids described by us [4].

Cyclization of these acids was studied under a variety of conditions. It was established that different reaction products — (3,5-dioxopiperazin-1-yl)alkylcarboxylic acids (VII-XII) and/or their amides (XIII-XV, XVII, XVIII) — were obtained depending on the temperature, the ratio of components, and the presence of a solvent.



I–VI VII–XII XIII–XVIII

I, VII R = CH_2COOH; II, VIII $CH(CH_3)COOH$; III, IX $C_6H_5CH_2CHCOOH$; IV, X $C_6H_5CHCH_2COOH$; V, XI $(CH_2)_3COOH$; VI, XII $(CH_2)_6COOH$; XIII $R^1 = CH_2CONH_2$; XIV $CH(CH_3)CONH_2$; XV $C_6H_5CH_2CHCONH_2$; XVI $C_6H_5CHCH_2CONH_2$; XVII $(CH_2)_3CONH_2$; XVIII $(CH_2)_6CONH_2$

In Table 1 are cited data on the dependence of the condensation products formed on the temperature, the ratio of components, and the solvent.

As in the case of cyclization of iminodiacetic acid [2], no cyclization products — piperazinediones-2,6 — were obtained at temperatures of 120-130°C: only the initial N-diacetic acids were isolated. When the temperature was raised to 150-160°C, the predominant products were the (3,5-dioxopiperazine-1-yl)alkanecarboxylic acids (VII-IX, XI, XII), but, depending on the duration of the reaction, the ratio of the components and the presence of solvent and small amounts of their amides were also isolated. When the temperature was raised to 180-190°C and the duration of the cyclization was increased the amides of the (3,5-dioxopiperazin-1-yl)alkane carboxylic acids (XIII-XV, XVII, XVIII) predominated. On boiling in DMF the corresponding alkanecarboxylic acids (VII-IX, XI and XII) were obtained. On condensation by fusion (method A) and when a solvent was used (method B), the optimal ratio of starting acid to ammonium formate was 1:3. A smaller amount of ammonium formate favored formation of the alkanecarboxylic acids (VII-IX, XI, XII), an increase in duration of the reaction and resinification of the reaction mixture.

The small yields (28-63%) of condensation products arise from decarboxylation of the acid starting materials at high temperature, difficulty of separating products (when two reaction products were formed) and losses in purification from oily impurities.

α-Alanin- (II) and β-phenyl-α-alanine-N-diacetic (III) acids are readily decarboxylated on heating [3]. It was shown that decarboxylation occurred as a result of the carboxyl group of the original amino acid and not the carboxyls of the

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0009-3122/98/3410-1185$20.00

TABLE 1. Conditions and Products of Cyclization

Compound	Molar ratio of reagents, acid:AF*	Temperature, °C	Duration of cyclization, h	Method	Cyclization products (yield, %)**
I	3 : 1	120...130	3	A	I
	1 : 1	150	2	B	VII
	1 : 1	150	7,5	B	VII (46,5)
	1 : 1	150	2	A	VII†
	1 : 1	150	7,5	A	VII (26,1), III†
	3 : 1	150	7,5	A	VII (11,0), II (23,0)
	3 : 1	150...185	3	A	VII†, XII (52,6)
II	3 : 1	150...160	3	B	VIII‡
	3 : 1	150...160	1	A	VIII†
	3 : 1	160...180	4	A	XIV
	3 : 1	160...180	14	A	XIV (33,6)
III	3 : 1	150...160	3	B	IX (28,2)
	3 : 1	150...180	2	A	IX†, XV
	3 : 1	150...180	3	A	IX, XV
	3 : 1	180...190	1,5	A	XV
	3 : 1	160...190	4	A	XV (41,9)
V	3 : 1	150...160	4	B	XI(45,3)
	1 : 1	150...160	1	A	—
	1 : 1	150...160	2	A	XI, XVIII†
	1 : 1	150...160	4	A	XI (30,0), XVIII†
	3 : 1	160...180	6	A	XI (19,3), XVIII (20,0)
VI	1 : 1	140...160	0,5	B	—
	1 : 1	140...160	1,0	B	XII†
	1 : 1	140...160	5	B	XII
	1 : 1	140...160	10	B	XII, XVIII†
	3 : 1	150...160	0,5	B	—
	3 : 1	150...160	1	B	XII†
	3 : 1	150...160	10	B	XII (45,0)
	3 : 1	150...160	0,5	A	—
	3 : 1	150...160	1,0	A	XII*
	3 : 1	150...160	2	A	XII
	3 : 1	150...160	5	A	XII, XVIII†
	3 : 1	150...160	10	A	XII (36,4), XVIII†
	3 : 1	160...190	4	A	XII†, XVIII (34,8)
	3 : 1	160...190	10	A	XVIII (45,0)

*Ammonium formate.

†Traces of substance (TLC).

‡Difficult to separate from oily impurities.

**Highest yields indicated.

iminodiacetic acid. On cyclization of these acids with ammonium formate at high temperatures, formation of 4-alkyl derivatives of piperazinedione-2,6, the products of cyclization of decarboxylated α-alanine- and β-phenyl-α-alanine-N-diacetic acids, were not observed (decarboxylation of N-diacetic α-amino acids evidently occurs by a mechanism other than that mentioned in [3]).

On condensation of α-alanine-N-diacetic acid with ammonium formate, only α-(3,5-dioxopiperazin-1-yl)propionamide was isolated and identified (XIV). A second cyclization product was observed by TLC (R_f 0.50, system I), but isolation and identification was unsuccessful. It may be assumed that this impurity is α-(3,5-dioxopiperazin-1-yl)propionic acid (VIII) which has an R_f value close to that of (3,5-dioxopiperazin-1-yl)acetic acid (VII).

TABLE 2. Characteristics of Compounds VII, IX, XI-XV, XVII, and XVIII

Compound	Molecular formula	Found, % / Calculated,			mp, °C (solvent)	R_f (TLC system)	Yield, %
		C	H	N			
VII	$C_6H_8N_2O_4$	41.74 41,86	4.73 4,65	16.10 16,26	185...187 (isopropanol)	0,53 (D)	46,5
IX	$C_{13}H_{14}N_2O_4$	59.38 59,54	5.29 5,38	10.40 10,68	186...188 (isopropanol)	0,74 (A)	28,2
XI	$C_8H_{12}N_2O_4$	48.11 47,99	6.02 6,04	13.97 13,99	128...130 (isopropanol)	0,83 (B)	30,0
XII	$C_{11}H_{18}N_2O_4$	54.50 54,53	7.50 7,49	11.53 11,56	103...105 (isopropanol)	0,83 (B)	36,4
XIII	$C_6H_9N_3O_3$	—	—	—	212...215 (ethanol – water) 216...218 [1]	0,39 (D)	52,6
XIV	$C_7H_{11}N_3O_3$	—	—	—	195...198 (ethanol – water)	0,65 (D)	33,6
XV	$C_{13}H_{15}N_3O_3$	59.90 59,76	5.48 5,79	15.99 16,08	200...202 (ethanol-water)	0,66 (B)	62,7
XVII	$C_8H_{13}N_3O_3$	48.20 48,23	6.45 6,58	21.09 21,10	149...152 (ethanol – water)	0,23 (B)	52,3
XVIII	$C_{11}H_{19}N_3O_3$	54.68 54,75	8,10 7,94	17.70 17,42	136...139 (ethanol – water)	0,48 (B)	45,0

TABLE 3. ^1H NMR Spectra of Compounds VII, IX, XI-XV, XVII, and XVIII

Compound	Chemical shifts, δ, ppm
VII	3,22 (2H, s, $COCH_2N$); 3,33 (4H, s, NCH_2CO); 10,96 (1H, br. s, NH)
IX	3,12 (2H, d, J = 6 Hz, CH_2); 3,31 (4H, s, NCH_2CO); 4,69 (1H, m, CH); 7,18 (5H, br. s, C_6H_5); 11,45 (1H, br. s, NH)
XI	1,61 (2H, q, J = 6 Hz, CH_2); 2,16 (2H, t, J = 7 Hz, CH_2N); 3,22 (4H, s, NCH_2CO); 11,03 (1H, br. s, NH)
XII	1,29 (10H, m, CH_2); 2,18 (2H, t, J = 7 Hz, CH_2N); 3,25 (4H, s, NCH_2CO); 11,05 (1H, br. s, NH)
XIII	3,00 (2H, s, $COCH_2N$); 3,31 (4H, s, NCH_2CO); 7,00, 7,28 (2H, br. s, NH_2); 11,00 (1H, br. s, NH)
XIV	1,21 (3H, d, J = 7 Hz, CH_3); 3,05 (4H, s, NCH_2CO); 3,42 (1H, q, J = 6 Hz, CH); 7,00, 7,28 (2H, br. s, NH_2); 11,05 (1H, br. s, NH)
XV	3,14 (2H, m, CH_2); 3,34 (4H, s, NCH_2CO); 3,69 (1H, m, CH); 6,70, 6,94 (2H, br. s, NH_2); 7,18 (5H, br. s, C_6H_5); 11,03 (1H, br. s, NH)
XVII	1,63 (2H, q, J = 5 Hz, CH_2); 2,01 (2H, t, J = 7 Hz, CH_2N); 2,36 (2H, t, J = 7 Hz, CH_2CO); 3,19 (2H, s, NCH_2CO); 3,25 (2H, s, NCH_2CO); 6,57, 7,13 (2H, br. s, NH_2); 11,05 (1H, br. s, NH)
XVIII	1,22 (10H, m, CH_2); 1,96 (2H, m, CH_2N); 3,22 (4H, br. s, NCH_2CO); 6,53, 7,09 (2H, br. s, NH_2); 11,03 (1H, br. s, NH)

When β-phenyl-β-alanine-N-diacetic acid (IV) was condensed with ammonium formate by melting (method A) or in DMF (method B) no derivatives of piperazindione-2,6 were obtained. The basic reaction product was cinnamic acid (R_f 0.90) plus an impurity (R_f 0.72). Cinnamic acid was isolated from the reaction mixture by sublimation and its structure was confirmed by ^1H NMR spectroscopy, elemental analysis, and its characteristic smell. Isolation of the second product from the very oily reaction mixture was not achieved. It may be suggested that it is β-(3,5-dioxopiperazin-1-yl)-β-phenylpropionic acid (X) since its R_f is close to that of α-(3,5-dioxopiperazin-1-yl)-β-phenylpropionic acid (IX). Decarboxylation of β-phenyl-β-alanine-N-diacetic acid (IV) occurred not only at high temperature in alkaline medium but also on heating at 150°C with or without DMF. Cinnamic acid was also the product of decarboxylation.

EXPERIMENTAL

Melting points of the synthesized compounds were determined with a Boetius block microheater. ^{1}H NMR spectra were recorded in DMSO-D_6 with HMDS as internal standard with a Hitachi R-22 (90 MHz) spectrometer. The course of reactions and the purity of compounds was monitored by TLC on Silufol-254 strips with elution by acetone–chloroform (1:1, system A), acetone–chloroform (3:1, system B), acetone–chloroform (1:3, system C) or chloroform–methanol (1:1, system D). Spots were revealed with a solution prepared from $CoCl_2 \cdot 6H_2O$) (1.83 g), $K_2Cr_2O_7$ (2 g), and glacial acetic acid (10 ml) in water (100 ml) (blue spots for cyclic imides). Elemental analysis results agreed with calculated values.

Yields and analytical characteristics of the compounds synthesized are given in Table 21 and their ^{1}H NMR spectra in Table 3.

General Method for the Cyclization of N-diacetic Amino Acids. A. A well-ground mixture of the N-diacetic amino acid and ammonium formate was heated on an oil bath. Completion of the condensation was determined by evolution of ammonia vapor (pH 9-10) and by TLC. The dark-colored reaction mixture was flooded with methanol and extracted for 12 h at −18°C. The residue was filtered off, washed with methanol, and dried. The corresponding cyclization products were obtained after treatment with activated carbon and recrystallization.

B. A mixture of the N-diacetic amino acid and ammonium formate was boiled in DMF. The course of the reaction was monitored by TLC. After condensation the DMF was evaporated in vacuum, the residue was flooded with methanol and extracted for 12 h at −18°C. The precipitated residue was filtered and washed with methanol. The corresponding cyclization product was obtained. When several condensation products were obtained, the reaction mixture was passed through a column of silica gel (Chemapol 40/100). Elution was with ethyl acetate or an acetone–chloroform mixture (3:1) (monitored by TLC).

REFERENCES

1. Brit. Pat. 1,170,399 (W. R. Grace Co. Ltd.); Chem. Abs., **72**, 54804 (1970).
2. P. Shvedaite, Khim. Geterotsikl. Soedin., No. 1, 73 (1995).
3. N. F. Kazarinova, N. I. Lamosh, and I. Ya. Postovskii, Izv. Sib. Otdel. Akad. Nauk SSSR, No. 2, 60 (1960).
4. I. P. Shvedaite, L. V. Chekuolene, and D. A. Kazlauskas, Tr. Akad. Nauk LitSSR, Ser. B, **2**, 35 (1984).