SYNTHESIS OF MODIFIED AMINO ACIDS CONTAINING NUCLEIC ACID PURINE BASES

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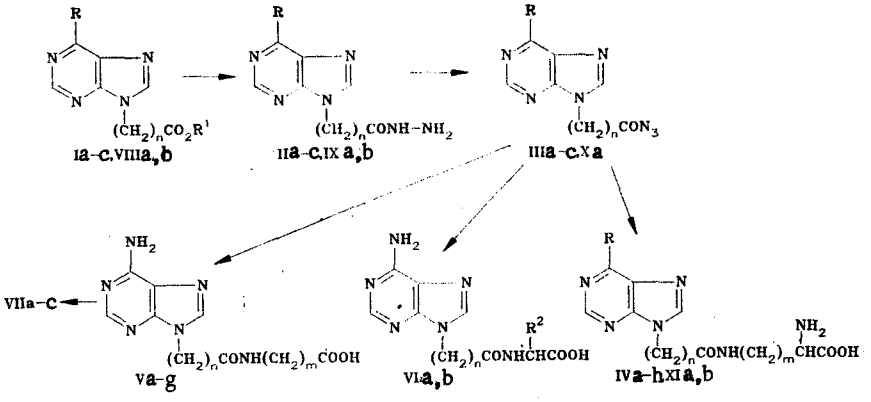
The reaction of hydrazides of adenylyl- or hypoxanthinyl-9-alkylcarboxylic acids with sodium nitrite in acid media gives reactive azides of purinyl-9-alkylcarboxylic acids which condense with α(ω)-aminocarboxylic and α,ω-diaminocarboxylic acids to give $N_\alpha(N_\omega)$-(adenylyl-9-alkanoyl)aminocarboxylic, N_α-(adenylyl-9-)- and N_ω-(hypoxanthinyl-9-alkanoyl)-α,ω-diaminocarboxylic acids. The deamination of N_ω-(adenylyl-9-alkanoyl)aminocarboxylic acids gives N_ω-(hypoxanthinyl-9-alkanoyl)aminocarboxylic acids.

In a continuation of a study of the synthesis and properties of purinyl-9-amino acids [1], we carried out the synthesis of $N_\alpha(N_\omega)$-(purinyl-9-alkanoyl)aminocarboxylic acids (V-VII) and N_α-(purinyl-9-alkanoyl)-α,ω-diaminocarboxylic acids (IV and XI). These compounds were synthesized by the azide method used in peptide chemistry. This method usually avoids racemization of the amino acids.

Esters of adenylyl-9-alkylcarboxylic acids I served as the starting compounds. The ethyl esters of adenylyl-9-acetic (Ia) and -propionic (Ib) acids were prepared according to Lira [2, 3]. To prepare the methyl ester of adenylyl-9-butyric acid Ic, we used a method based on the alkylation of adenine by the methyl ester of γ-chlorobutyric acid, which is more convenient than the method described by Chakrabotri [4].

The hydrazides of adenylyl-9-alkylcarboxylic acids II were prepared by treatment of a concentrated ethanolic solution of esters I with a tenfold excess of hydrazine hydrate (in order to exclude formation of the bishydrazides) at room temperature. The yields of hydrazides II were 95% on the average.



I—III, VII—IX a n=1, b n=2; Xa, XIa, XIb n=1; IV, V a—c n=1, d—f n=2; IVg, VIIc n=2; Ic—IIIc, IVh, Vg n=3; IVa,e, VIIb, XIa m=2, IVb,f,h, VIIa,c, XIb m=3, c,g, m=4,d m=1; V a,d m=2, b,e,g m=3, c,f m=5; VI a n=2, $R^2=CH_2CH(CH_3)_2$; b n=3, $R^2=CH_2C_6H_5$; I, VIII a, b $R^1=C_2H_5$; I c $R^1=CH_3$; Ia—c—IIIa—c, IVa—h R=NH_2, VIIIa, b—XIa, b; Xa R=OH

The reactive azides of adenylyl-9-alkylcarboxylic acids IIIa-c were prepared by the action of nitrous acid on the corresponding hydrazides IIa-c. Adenylyl-9-carboxylic acid azides IIIa-c are unstable and rearrange to the corresponding isocyanates as indicated by comparison

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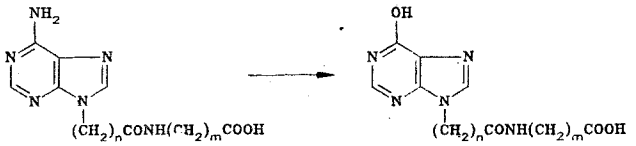
of the IR spectra taken at given time intervals. After 24 h, the IR spectra show the gradual disappearance of the band at 2140 cm^{-1} characteristic for the asymmetric stretching vibrations of the $-N=N=N=N$ group and the appearance of a new band for the $-N=C=O$ group at 2280 cm^{-1}.

In order to prevent side-reactions, the sodium nitrite was added to a hydrochloric acid solution of adenylyl-9-alkylcarboxylic acid hydrazide at reduced temperature. The precipitated azide III was not subjected to further purification but rather immediately condensed with the corresponding amino component under the usual Schotten–Baumann conditions. We used α,ω-diamino acids, α-amino acids, and ω-amino acids as the amino component.

N_α-(Adenylyl-9-alkanoyl)aminocarboxylic acids VIa and VIb and N_ω-(adenylyl-9-alkanoyl)-α,ω-diaminocarboxylic acids IVa-h were separated from the reaction mixture using ion-exchange chromatography on a Dowex 1 × 8 ($HCOO^-$) resin column, while N_α-(adenylyl-9-alkanoyl)aminocarboxylic acids Va-g were precipitated from the reaction mixture by the addition of acetic acid to pH 5.



Vb,d,c VIIa-c

Vb, VIIa n=1; Vd,e, VIIb,c n=2; Vd, VIIb m=2; Vb,e, VIIa,c m=3

N_ω-(Hypoxanthinyl-9-alkanoyl)aminocarboxylic acids VIIa-c were obtained by the action of sodium nitrite on a suspension of N_ω-(adenyl-9-alkanoyl)aminocarboxylic acids V in acetic acid at room temperature. The reaction is conveniently monitored by UV spectroscopy. Upon the conversion of adenine derivatives to hypoxanthine derivatives, the UV spectra taken in acid media show a hypsochromic shift of the absorption maximum by about 10 nm. Hypoxanthine derivatives VIIa-c were isolated from the reaction mixture by chromatography on a Dowex 1 × 8 ($HCOO^-$) ion-exchange resin column.

N_ω-(Hypoxanthinyl-9-alkanoyl)-α,ω-diaminocarboxylic acids XIa and XIb were synthesized analogously to the above method for the preparation of adenine derivatives IV. Esters of hypoxanthinyl-9-alkylcarboxylic acids VIIIa and VIIIb prepared by the deamination of the corresponding adenine derivatives Ia and Ib were used as the starting compounds. The reaction of esters VIIIa and VIIIb with hydrazine hydrate gave hydrazides IXa and IXb, which, upon the action of nitrous acid, gives the corresponding azides Xa and Xb. These azides, in turn, react with L-α,ω-diamino acids to form amino acid derivatives XIa and XIb which were isolated by chromatography on a Dowex 1 × 8 ($HCOO^-$) ion-exchange resin column.

The structures of the amino acid derivatives prepared were supported by the UV and IR spectra, acid hydrolysis and elemental analysis. In addition to the purine ring bands, these IR spectra show a strong band for amide II at 1570-1560 and 1250 cm^{-1} due mainly to the N–H deformation vibrations and C–N stretching vibrations. The band at 3340-3320 cm^{-1} was assigned to secondary amide group N–H stretching vibrations.

All the modified amino acids containing purine bases which are reported in this work are high-melting crystalline compounds with intense absorption in the near UV.

EXPERIMENTAL

The UV spectra were taken on a Spetromom-204 spectrometer in 0.1 N hydrochloric acid, water, and 0.1 N aq. NaOH. The IR spectra were taken on a UR-20 spectrophotometer in vaseline oil. The specific rotations were measured on a Perkin-Elmer 141 polarimeter. The reaction course and purity of the compounds prepared were monitored by thin-layer chromatography on Silufol plates with eluents: 7:1:2.2 2-propanol–25% aqueous ammonia–water, 2) water, 3) 6:4:4 butanol–acetic acid–water, and 4) 7:3 ethanol–water. The compounds were detected on the chromatograms by UV light and developed using ninhydrin.

Hydrazide of Adenylyl-9-acetic Acid (IIa). A sample of 5 g (100 mmoles) hydrazine hydrate was added to a concentrated solution of 2.2 g (10 mmoles) ethyl ester of adenylyl-9-

acetic acid Ia in ethanol. The mixture was stirred at room temperature for 3-4 h and left overnight. The precipitated hydrazide IIa was filtered off and crystallized from ethanol—water (Table 1).

Hydrazide of adenylyl-9-propionic Acid (IIb) and hydrazide of adenylyl-9-butyric acid (IIc) were obtained analogously to IIa from the corresponding starting compounds (Table 1).

N_γ-(Adenylyl-9-acetyl)-α,γ-diaminobutyric Acid (IVa). A sample of 8 ml hydrochloric acid was added to a suspension of 2.2 g (10 mmoles) hydrazide IIa in 30 ml water. The solution was cooled to 0-5°C and a concentrated aqueous solution of 2.1 g (30 mmoles) acid IIIa was filtered off and gradually added with stirring to a solution of 1.9 g (10 mmoles) dihydrochloride salt of L-α,ω-diaminobutyric acid in 20 ml 1 N aq. NaOH cooled to 0-5°C. The solution was maintained at room temperature for 2 h and then concentrated in vacuum to one-third volume. The solution pH was brought to 9 by the addition of acetic acid. The solution was placed on a Dowex 1 × 8 ($HCOO^-$) ion-exchange resin column and washed with water until a negative probe was obtained with ninhydrin. Product IVa was eluted with 0.1 N formic acid. The eluate was evaporated in vacuum to dryness with bath temperature to 35°C. Precipitated IVa was washed with ethanol and ether (Table 2).

N_δ-(Adenylyl-9-acetyl)ornithine (IVb), N_ε-(adenylyl-9-acetyl)lysine (IVc), N_β-(adenylyl-9-propionyl)-α,β-diaminopropionic acid (IVd), N_γ-(adenylyl-9-propionyl)-α,γ-diaminobutyric acid (IVe), N_δ-(adenylyl-9-propionyl)ornithine (IVf), N_δ-(adenylyl-9-propionyl)lysine (IVg), and N_δ-(adenylyl-9-butyryl)ornithine (IVh) were obtained analogously to IVa from the corresponding starting compounds (Table 2).

N_β-(Adenylyl-9-acetyl)-β-alanine (Va). A sample of azide IIIa was added with stirring to a solution of 0.89 g (10 mmoles) β-alanine in 30 ml 1 N aq. NaOH cooled to 0-5°C. The solution was maintained at room temperature for 2-3 h and then brought to pH 5-6 by the addition of acetic acid. The mixture was left at 0°C overnight. The precipitate was filtered off, washed with water and crystallized from water (Table 2).

N_γ-(Adenylyl-9-acetyl)aminobutyric acid (Vb), N_ε-(adenylyl-9-acetyl)aminocaproic acid (Vc), N_β-(adenylyl-9-propionyl)-β-alanine (Vd), N_γ-(adenylyl-9-propionyl)aminobutyric acid (Ve), N_ε-(adenylyl-9-propionyl)aminocaproic acid (Ve), and N_γ-(adenylyl-9-butyryl)aminobutyric acid (Vg) were obtained analogously to Va from the corresponding ω-amino acids and azides (Table 2).

N-(adenylyl-9-propionyl)leucine (VIa) and N-(adenylyl-9-butyryl)phenylalanine (VIb) were obtained from the corresponding L-α-amino acids and hydrazides IIb and IIc by analogy with IVa.

N_γ-(Hypoxanthinyl-9-acetyl)aminobutyric Acid (VIIa). A saturated aqueous solution of 0.35 g (5 mmoles) sodium nitrite was added to a suspension of 0.28 g (1 mmole) acid Vb in 12 ml glacial acetic acid and maintained in a closed flask at room temperature for two days. The solution formed was evaporated to dryness. Water was added to the residue and the mixture was again evaporated until the reaction solution was neutral. The solution pH was then brought to 9 by the addition of aqueous ammonia. Reaction product VIIa was separated analogously to IVa (Table 2).

N_β-(Hypoxanthinyl-9-propionyl)-β-alanine (VIIb) and N_γ-(hypoxanthinyl-9-propionyl)aminobutyric acid (VIIc) were obtained analogously to VIIa from the corresponding starting compounds (Table 2).

TABLE 1. Hydrazides of Adenylyl-9- (IIa-c) and Hypoxanthinyl-9-carboxylic Acids (IXa, b)

Compound	R_f				mp, °C	Found, %			Chemical formula	Calculated, %			Yield, %
	1	2	3	4		C	H	N		C	H	N	
IIa	0,64	0,32	0,13	0,39	296	40,2	4,4	46,7	$C_7H_9N_7O$	40,6	4,4	47,3	96
IIb	0,70	0,20	0,08	0,27	284	43,3	5,0	43,8	$C_8H_{11}N_7O$	43,4	5,0	44,3	99
IIc	0,73	0,14	0,07	0,24	230—231	46,2	5,5	41,2	$C_9H_{13}N_7O$	46,0	5,6	41,7	87
IXa	0,55	0,60	0,15	0,48	287—288	40,1	3,8	41,0	$C_7H_8N_6O_2$	40,4	3,9	40,4	93
IXb	0,60	0,45	0,10	0,43	254—255	43,0	4,4	37,3	$C_8H_{10}N_6O_2$	43,2	4,5	37,8	75

TABLE 2. Characteristics of Compounds Synthesized IVa-h, Va-g, VIa,b, VIIa-c, and XIa, b

Compound	R_f			mp, °C	$[\alpha]_D^{20}$, deg (c=1.0; H_2O)	Found, %			Chemical formula	Calculated, %			Yield, %
	1	2	3			C	H	N		C	H	N	
IVa	0,67	0,32	0,15	234—236	+17,7	45,5	5,6	33,2	$C_{11}H_{15}N_7O_3$	45,1	5,2	33,4	30
IVb	0,70	0,30	0,13	258—260	+3,6	47,5	5,9	32,3	$C_{12}H_{17}N_7O_3$	46,9	5,6	31,9	26
IVc	0,65	0,27	0,10	252—254	+2,1	46,5	5,9	29,0	$C_{13}H_{19}N_7O_3\times H_2O$	46,0	6,2	28,9	28
IVd	0,68	0,28	0,12	240—243	−2,6	45,6	5,6	33,0	$C_{11}H_{15}N_7O_3$	45,1	5,2	33,4	29
IVe	0,63	0,27	0,10	217—219	−8,2	44,6	5,5	30,5	$C_{12}H_{17}N_7O_3\times H_2O$	44,3	5,9	30,1	34
IVf	0,66	0,26	0,15	235—236	+2,9	47,8	6,3	29,5	$C_{13}H_{19}N_7O_3\times 1/2H_2O$	47,3	6,1	29,7	26
IVg	0,62	0,25	0,12	226—227	+2,4	47,5	6,4	27,5	$C_{14}H_{21}N_7O_3\times H_2O$	47,6	6,5	27,8	30
IVh	0,64	0,28	0,15	234—236	−3,4	50,0	6,6	28,4	$C_{14}H_{21}N_7O_3$	50,1	6,3	29,2	24
Va	0,72	0,75	0,48	310—311	—	45,8	4,3	31,3	$C_{10}H_{12}N_6O_3$	45,5	4,6	31,8	45
Vb	0,72	0,74	0,53	299—300	—	48,0	5,2	29,7	$C_{11}H_{14}N_6O_3$	47,5	5,1	30,2	38
Vc	0,81	0,77	0,73	269—270	—	47,8	6,2	25,4	$C_{13}H_{18}N_6O_3$	48,1	6,2	25,9	37
Vd	0,72	0,75	0,47	262—264	—	46,9	4,8	30,0	$C_{11}H_{14}N_6O_3$	47,5	5,1	30,2	50
Ve	0,74	0,75	0,50	253—255	—	46,7	5,6	27,5	$C_{12}H_{16}N_6O_3\times H_2O$	46,5	5,8	27,1	70
Vf	0,82	0,75	0,76	251—253	—	50,3	6,7	24,8	$C_{14}H_{20}N_6O_3$	49,7	6,6	24,8	37
Vg	0,74	0,77	0,51	265—266	—	50,0	5,8	26,7	$C_{13}H_{18}N_6O_3\times 1/2H_2O$	49,5	6,1	26,7	80
VIa	0,85	0,83	0,39	256	−119,3*	47,9	6,5	24,4	$C_{14}H_{20}N_6O_3\times 1,5H_2O$	48,4	6,7	24,2	34
VIb	0,70	0,78	0,27	243—244	−42,0*	58,2	5,7	23,0	$C_{18}H_{20}N_6O_3$	58,7	5,5	22,8	32
VIIa	0,62	0,73	0,52	249—251	—	45,0	4,8	24,0	$C_{11}H_{13}N_5O_4\times H_2O$	44,5	5,1	23,6	63
VIIb	0,64	0,71	0,45	241—243	—	45,1	4,4	23,9	$C_{11}H_{13}N_5O_4\times 1/2H_2O$	45,8	4,9	24,3	60
VIIc	0,63	0,71	0,48	157—160	—	48,8	5,6	23,5	$C_{12}H_{15}N_5O_4$	49,1	5,2	23,9	50
XIa	0,80	0,52	0,10	211—213	−4,2	46,4	5,4	26,8	$C_{12}H_{16}N_6O_4$	46,8	5,2	27,3	35
XIb	0,82	0,50	0,10	189—192	−3,5	48,8	5,9	25,8	$C_{13}H_{18}N_6O_4$	48,4	5,6	26,1	40

*In 0.01 N NH_4OH.

Ethyl ester of hypoxanthinyl-9-acetic acid (VIIIa), was obtained from the ethyl ester of adenylyl-9-acetic acid Ia by analogy to VIIa. The solution formed was evaporated in vacuum to dryness, the residue was washed with water and crystallized from water. The product yield was 84.8% mp 231°C, R_f (system): 0.65 (1), 0.68 (4), 0.2 (3). UV spectrum: λ_{max}: 249 (pH 1), 248 (pH 7), 255 nm (pH 13). Found: C 48.4; H 4.8; N 24.9%. Calculated for $C_9H_{10}N_4O_3$: C 48.7; H 4.5; N 25.2%.

Ethyl ester of hypoxanthinyl-9-propionic acid (VIIIb) was prepared from ester Ib analogously to VIIa in 63% yield, mp 184-185°C. R_f (system): 0.63 (1), 0.62 (4), 0.18 (3). UV spectrum, λ_{max}: 249 (pH 1), 248 (pH 7), 255 nm (pH 13). Found: C 51.2; H 5.4; N 23.9%. Calculated for $C_{10}H_{12}N_4O_3$: C 50.8; H 5.1; N 23.7%.

Hydrazide of hypoxanthinyl-9-acetic acid (IXa) was prepared from VIIIa analogously to IIa (Table 1).

Hydrazide of hypoxanthinyl-9-propionic acid (IXb) was prepared from ester VIIIb by analogy to IIa (Table 1).

N_γ-(Hypoxanthinyl-9-acetyl)-α,γ-diaminobutyric acid (XIa) and N_δ-(hypoxanthinyl-9-acetyl)-ornithine (XIb) were obtained analogously to IVa from hydrazide IXa and the corresponding diamino acids (Table 2).

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