ACYLATION OF POLYMETHYLENEDIAMINES BY 3-(1-URACILYL)PROPIONIC ACID

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The reaction of pentafluorophenyl 3-(1-uracily1) propionate with polymethylenediamines gives N, N'-bix[3-(1-uracily1)) propiony1] polymethylenediamines.

Continuing the work begun in [1] on the synthesis of modified biogenic amines, we synthesized a number of N,N'-bis[3-(1-uracily1)propiony1]polymethylenediamines, which are of interest as potential physiologically active substances.

In the last few years, a number of acylated derivatives of spermidine, for example, N-(3-methyldodecanoyl)spermidine [2], which has antitumor activity, and N-[3-(3,4-dihydroxy-l-phenyl)propionyl]spermidine, which has antihypertensive properties [3], have been isolated from natural objects. Spermidine also appears in the structure of a broad-spectrum antibiotic, which was isolated from the genus *Nocardia* [4]. Synthetic N,N'-bis(haloacyl) derivatives of polymethylenediamines have antimicrobial activity [5].

Acylated derivatives of polymethylenediamines have hitherto been obtained mainly by reacting polymethylenediamines with acid halides or methyl esters of carboxylic acids [5-7]. In these cases, both amino groups react to form N,N'-bisacylated diamines. When spermidine is acylated, a mixture of mono-, di-, and triacetylated derivatives, which is difficult to separate, forms [8]. The reaction of spermidine with cinnamoyl chloride results mainly in the formation of a mixture of the N¹,N⁴- and N⁴,N⁸-bisacylated products. N¹,N⁸-Bisacylated spermidine was isolated with a yield smaller than 5% [9]. This is attributed to the fact that the secondary amino group reacts with most electrophilic reagents more readily than do the terminal primary amino groups [10].

As a starting compound we used pentafluorophenyl 3-(1-uracilyl)propionate, which was obtained by reacting 3-(1-uracilyl)propionic acid with pentafluorophenol. The reaction of ester I with an equimolar quantity of diamines takes place at room temperature, and both amine groups in the diamine react in this case. An attempt to obtain the monosubstituted



II a $A = -(CH_2)_4 - ;$ b $A = -(CH_2)_5;$ c $A = -(CH_2)_6 - ;$ d $A = -(CH_2)_3 - NH - (CH_2)_4 - ...$

diamine by altering the ratio between the reaction components was unsuccessful. A monosubstituted diamine was recovered with a 6% yield only in the case of the reaction of putrescine with ester I, whereas in the remaining cases, the monosubstituted products were detected in the form of an impurity (less than 1%) with the aid of TLC. In the case of the reaction of activated ester I with spermidine, only N^1, N^8 -bisacylated spermidine (IId) was isolated with a good yield, regardless of the ratio between the reaction components.

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TABLE 1. Proton-Magnetic-Resonance Spectra of N,N'-Bis[3-(1uracily1)propiony1]polymethylenediamines IIa-d and III

Com- pound	Chemical shifts, ppm					
	NH, s	6-H, d	5-H,d	α-CH ₂ , c	β -CH ₂ , t	aliphatic chain
IIa	10,95	7,39	5,37	3,65	2,35	3,00 (4H, m, 1-, 4-CH ₂); 1,45 (4H, m, 2-, 3-CH ₂)
Цb	10,95	7,40	5,40	3,65	2,45	3,10 (4H, m, 1-, 5-CH ₂); 1,60 (2H, m, 3-CH ₂);
Πc	10,94	7,39	5,42	3,77	2,44	1,40 (4H, m 2-, 4-CH ₂) 3,05 (4H, m, 1-, 6-CH ₂); 1,60 (4H, m, 2-, 5-CH ₂);
l I d	10,05	7,42	5,41	3,84	2,44	3,04—3,4 (4H, m, CONHCH ₂); 2,52 (4H, m, CH ₂ NHCH ₂); 1,53 (2H, m, NHCH ₂ — CH ₂ CH ₂ NH); 1,35 (4H, m,NHCH ₂ CH ₂ CH ₂ -
III	10,95	7,40	5,39	3,70	2,52	3,15 (2H, m 1-CH ₂); 2,55 (2H, m, 4-CH ₂); 1,55 (4H, m, 2-, 3-CH ₂)

The structures of diamides IIa-d and of amide III were confirmed by the data from the UV, IR, and PMR spectra. In the IR spectra, besides the absorption bands which are assigned to the uracil ring and the amide I bands ($1700-1670 \text{ cm}^{-1}$), there is a strong amide II absorption band at 1570-1560 and at 1250 cm⁻¹, which is caused mainly by the deformation vibrations of the N-H group and the stretching vibrations of the C-N group. The absorption band at 3370-3350 cm⁻¹ is assigned to stretching vibrations of the N-H group in secondary amides.

The structures of compounds II and III are confirmed by the data from the PMR spectra. The ratio between the integrated intensities of the signals of the protons on $C(_5)$ and $C(_6)$ in the uracil ring and the signals of the protons in the individual methylene groups in the aliphatic chain of the diamines and spermidine attests to the presence of two uracil rings in the molecules of amides IIa-d.

Amides IIa-d do not show the color reaction with ninhydrin which is characteristic of a primary amino group. Amide III gives the violet color characteristic of a primary amino group with ninhydrin.

The individuality of amides IIa-d and III was confirmed by the data from TLC.

EXPERIMENTAL

The IR spectra were recorded on a UR-20 instrument in liquid petrolatum, the UV spectra were recorded on a Spectromom 204 instrument in water (pH 7), and the PMR spectra were recorded on a Bruker instrument (90 and 360 MHz) in DMSO-de with HMDS as an internal reference. The course of the reaction and the individuality of the compounds obtained were monitored with the aid of TLC on Silufol UV-254 plates in a 7:1:2 isopropanol-ammonia-water system. The compounds were detected on the chromatograms according to the absorption of the UV rays, and the compounds containing a primary amino group were exposed by ninhydrin.

<u>3-(1-Uracily1) propionic acid</u> is obtained by the acid hydrolysis of methyl 3-(1-uracily1)-propionate, which, in turn, is obtained from uracil and methyl acrylate under conditions similar to those in [11]. The yield is 81%, and the mp is $183-186^{\circ}$ C [12].

Pentafluorophenyl 3-(1-Uracily1)propionate (I). A solution of 8.1 g (4.5 mmole) of 3-(1-uracily1)propionate in 200 ml of DMFA at 0°C is given an addition with stirring of 40.8 g (5 mmole) of complex F (the complex of dicyclohexylcarbodiimide and pentafluorophenol). The stirring is continued for 3 h, and the reaction mixture is held for 12 h at 4°C. A 0.1-ml portion of glacial acetic acid is added, and the precipitate of dicyclohexylurea is filtered out. The filtrate is evaporated in a vacuum to dryness. The residue is dissolved in 30 ml of ethyl acetate. The solution is washed successively with water, 2 N hydrochloric acid, a 0.5 N solution of sodium bicarbonate, and water and dried over Na₂SO₄. The mixture is filtered, the filtrate is evaporated in a vacuum to dryness, and the residue is reprecipitated from ethyl acetate by ethyl ether. The yield is 13.8 g (89.6%), and the mp is 151-152°C. Found: C, 45.3; H, 2.5; N, 8.2%. Calculated for $C_{13}H_7F_5N_2O_4$: C, 44.6; N, 2.0; N, 8.0%.

<u>N,N'-Bis[3-(1-uracily1)propiony1]tetramethylenediamine (IIa).</u> A solution of 2.1 g (0.6 mmole) of ester I in 200 ml of ethylacetate is given an addition with stirring of a solution of 0.53 g (0.6 mmole) of tetramethylenediamine in 5 ml of DMFA. The mixture is stirred for 30 min, and the precipitate formed is filtered out and washed with ethanol. The yield is 1.4 g (55.9%), and the mp is $253-255^{\circ}C$ (water). IR spectrum 1690, 1650 (CO), 1550, 1250,

3310 cm⁻¹ (NH). UV spectrum (H₂O), λ_{max} (log ϵ): 266 nm (4.15). Rf 9.6. Found: C, 50.7; H, 5.8; N, 19.2%. Calculated for C₁₈H₂₄N₆O₆: C, 51.4; H, 5.8; N, 20.0%.

The filtrate is concentrated to a small volume and N-[3-(1-uracily1)propiony1]tetramethylenediamine (III) is precipitated by ether. The yield is 0.1 g (6.6%), and the mp is 182-184°C. IR spectrum: 1700, 1640 (CO), 1150 (C-N), 1560, 1260, 3310 cm⁻¹ (NH). Found: C, 52.0; H, 6.8; N, 21.5%. Calculated for $C_{11}H_{18}N_4O_3$: C, 51.4; H, 5.8; N, 20.0%.

<u>N,N'-Bis[3-(1-uracily1)propionyl]pentamethylenediamine (IIb)</u> is obtained from ester I and pentamethylenediamine in analogy to compound IIa. The yield of the amide is 68%, and the mp is 222-223°C (water). UV spectrum (in H₂O), λ_{max} (log ε): 266 nm (4.18). Rf 0.83. IR spectrum: 1660, 1700 (CO), 1250, 1540, 3308 cm⁻¹ (NH). Found: C, 52.4; H, 6.2; N, 19.5%. Calculated for C_{19H26N6}O₆: C, 52.5; H, 6.0; N, 19.3%.

<u>N-N'-Bis[3-(1-uracily1)propiony1]hexamethylenediamine (IIC)</u> is obtained from ester I and hexamethylenediamine in analogy to compound IIa. The yield is 79%, and the mp is 228-230°C (water). UV spectrum (in water), λ_{max} (log ε): 266 nm (4.15). Rf 0.71. IR spectrum: 1630, 1670, 1700 (CO), 1230, 1260, 1560, 3310, 3315 cm⁻¹ (NH). Found: C, 51.7; H, 6.0; N, 18.4%. Calculated from C₂₀H₂₈N₆O₆·H₂O: C, 51.5; H, 6.5; N, 18.0%.

 $\frac{N^{1},N^{8}-Bis[3-(1-uracilyl)propionyl]spermidine (IId) is obtained in analogy to amide IIa from ester I and spermidine. The yield of IId is 64.8%, and the mp is 82-85°C (methanol). UV spectrum (water), <math>\lambda_{max}$ (log ε): 266 nm (4.12). Rf 0.4. IR spectrum: 1640, 1670, 1700 (CO), 1205, 1560, 3300 cm⁻¹ (NH). Found: C, 53.5; H, 6.4; N, 19.2%. Calculated from C₂₁H₃₁N₇O₆: C, 52.8; H, 6.6; N, 20.5%.

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