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REGIOSPECIFIC SYNTHESIS OF MONO- OR DIACETYLATED POLYETHYLENEPOLYAMINE DERIVATIVES

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Abstract: Acetylated polyethylenepolyamines $CH_3CONHCH_2(CH_2\text{-}NH\text{-}CH_2)_nCH_2NH_2$ (n=1,2;) were synthesized using α-D-pentaacetyl-glucose as an acetylating agent.

Polyamines may represent the structural skeleton of a variety of important naturally occurring compounds [1-4]. Certain chemically modified linear polyamines and their carboxylic acids form stable chelates with various metal ions.

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These polyamines have found use in chemical, biological and medical research as tumor-specific radiopharmaceuticals [5-8], antituberculosis agents [9,10], fluorescent tracers in immunoassays [11,12], and as chelate surfactants for the removal of heavy metals from contaminated surfaces [13]. In most cases, their syntheses require the selective monoacylation of a single primary amino group. Using diamines but not polyamines, the common methods for monoacylation, mostly resulted in a mixture of monoamide, diamide and unreacted material. The degree of success was generally low [14-26].

Several mechanisms for the observed formation of abnormally large amounts of diacyl material have been considered. A proposed mechanism of intramolecular catalysis has been favored for some time [14, 23-25]. It was suggested that the first formed amido group rendered the other primary amino group of the monoamide more reactive than the amino groups of the nonacylated diamine. However, inconsistent with this view, kinetic studies showed that the reaction with the second primary amino group was slower, not faster, than that with the first one [27]. The fact, that N,N-dimethyl derivatives are acylated faster than the parent diamines favors a proposed mechanism of intramolecular general base catalysis by the second amino group but not the amido group.

The substitution at only one amino terminal of polyalkylenepolyamines is much more difficult than acylation

of diamines. Also, in polyamines, the spacings between the primary amino groups may contain elements other than simple hydrocarbon units, and this renders the reaction mechanism much more complex [28-30]. As a result, the monoacylation of polyamines is not readily described in the chemical literature. Only the formation of monoacetyltriethylene-tetramine by treatment of triethylene-tetraamine with 3.5 equivalents of ethyl acetate has been reported, but the product was not well characterized [30].

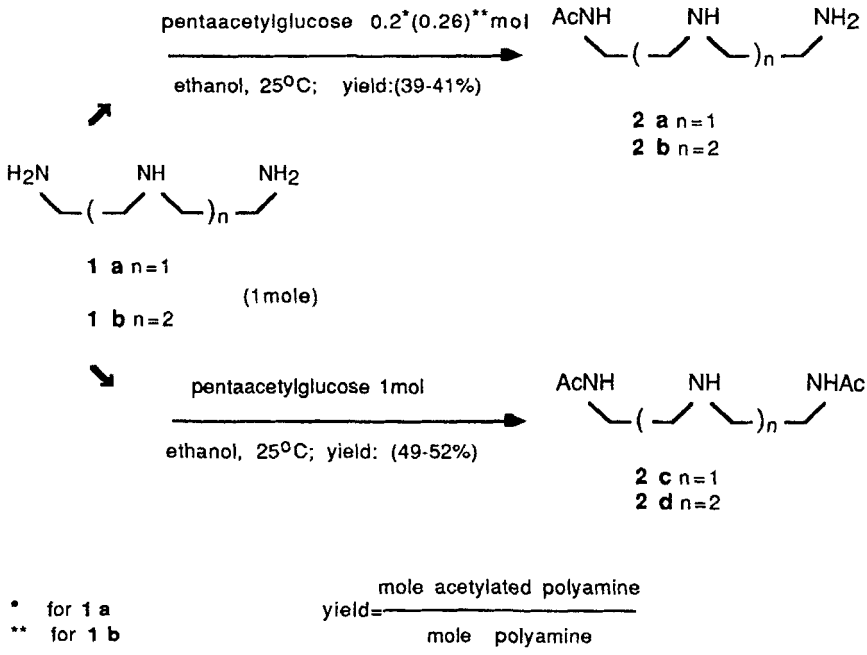
It was the purpose of this study to find a mild acetylating agent that would react with polyethylene-polyamines to form mono- or diacetylated polyamines in high yield and easily separable form.

Results and Discussion Section

In the present paper, we report a method for the selective synthesis of either mono- or diacetylated diethylenetriamine (**1a**) and triethylenetetraamine (**1b**). The method involves the reaction of a mild acetylating agent (α-D-penta-O-acetylglucose) with the respective polyamine.

Previous studies indicated, that the reaction of aromatic or aliphatic amines with pentaacetylated saccharides appeared to produce amino or acetamidosugars [31-33]. In addition, the formation of acetylated amines has been reported in reactions of acetylated sugars with monoamine, but such a reaction was not applied to the acetylation of polyamines [31].

SCHEME I



* for **1 a**
** for **1 b**

$$\text{yield} = \frac{\text{mole acetylated polyamine}}{\text{mole polyamine}}$$

It was found that, depending on the ratio used, this reagent produced mono- or disubstituted polyethylene-polyamines. The desired monoacetylated polyamines were obtained by reaction of the polyamine with pentaacetylglucose at a ratio of 3 equivalents of amine to 1 equivalent of acetyl. After isolation of the amido polyamine, the remaining amino groups were then available for other substitution reactions, for example the preparation of carboxymethyl esters by treatment with ethylbromoacetate in the presence of triethylamine. The described monoacetylation then serves as

Table I

Preparation of Mono- or Diacetylated Polyamines

Product	molar ratio [a]	equiv.acetyl-/equiv.amine [b]	Yield, % [c]	n_D^{20}	mp °C)
2a	0.20	0.30	41	1.5046	
2b	0.26	0.30	39		111-112
2c	1.00	1.67	52	1.4974	
2d	1.00	1.25	49		150-152

(a) moles of α-penta-O-acetylglucose used per mole of polyamine
(b) equivalents of acetyl- used per equivalent of amine
(c) yield based on original polyamine converted to acetylated polyamine

an example for a protection reaction that allows other substitution reactions to be carried out on other amino groups of the polyamines. At a larger ratio of NH_2: acetyl-, increasing yields of the diacetylated amine were obtained. A general outline of the preparation of several monoacetylated polyamines is shown in Scheme 1.

The results of several reactions between polyamines **1a-b** and α-D-penta-O-acetylglucose are presented in Table I.

When the reactions were carried out with less than one equivalent of acetyl /total of all amine groups, the yields of monoacetylated amine **2a** and **2b** were 41 and 39%,

respectively. Diacetylated derivatives **2c** and **2d** were not detected in the reaction mixture. The reaction is specific only for polyamines. When one or more nitrogens of the secondary amino groups were substituted by oxygen to form (poly)oxapolyamines, the product contained a mixture of mono- and diamidopolyamines.

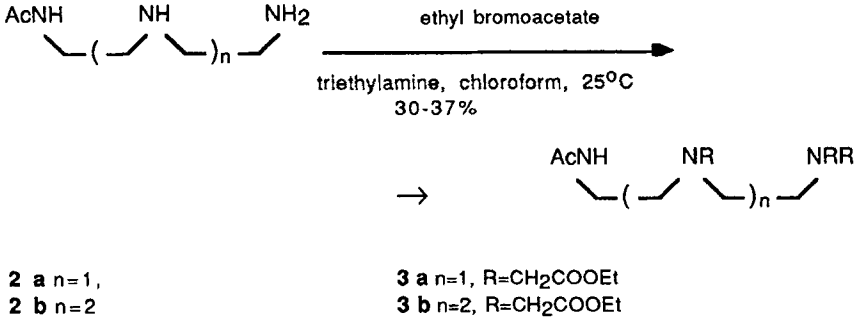
With an excess of acetyl groups, **1a** and **1b** gave diacetyl derivatives **2c** and **2d** with a yield of 52 and 49%, respectively. Treatment of previously isolated mono-acetylated polyamines with pentaacetylglucose also gave diacetylated products.

The method presented is very useful for the mono-substitution of polyamines and yields a single product, either mono- or disubstituted, depending on the ratio of the reagents used.

The usefulness of such (intermediate) monosubstitution as a protection reaction is demonstrated by the selective substitution of a monoacetylated polyamine with ethyl bromoacetate in the presence of triethylamine which yielded the polycarboxymethylated derivatives shown in Scheme II.

Compounds **3a** and **3b**, for instance, can be transformed by base hydrolysis to polycarboxylic acids, bifunctional chelating agents. The structures of **3a** and **3b** were

SCHEME II



2 a n=1,
2 b n=2

3 a n=1, R=CH_2COOEt
3 b n=2, R=CH_2COOEt

established by NMR and confirmed mono- or disubstitution as well as the positions of acetyl group.

Experimental Section

Starting materials were obtained from commercial suppliers. They were used without further purification. Flash chromatography on silica gel, Merck 230-400 mesh, was performed for purification. Polyester or glass plates with silica gel 60 F254 served for thin-layer chromatography. Iodine and molybdenepolyphoshoric acid were used for visualization. Melting points were determined on a Reichert Hot Stage apparatus and are uncorrected. The following mixtures of solvents were used:

A. chloroform, propanol, methanol, ammonia = 5:2:2:1
B. chloroform, methanol = 9:1
C. acetone, methanol = 9:1

General Procedure for the Preparation of Acetylated Polyamines (2).

Solid α-D-penta-O-acetylglucose (3.33 g, 8.54 mmol) was added to the solution of (4.4 g, 42.7 mmol) diethylenetriamine (**1a**) in 57 ml ethanol. The resulting reaction mixture was stirred for 20 hours at room temperature. Solvent was evaporated under reduced pressure to dryness. The crude product containing unreacted diethylenetriamine was purified by flash chromatography over silica gel (solvents: chloroform followed by A).

N-Acetyl-3-azapentane-1,5-diamine (2a):

2a is a colorless, oily substance. TLC (A) R_f = 0.35; n_D^{20}=1.5046; IR (film) 1660, 1579 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.28 (q, 2H), 2.58-2.79 (m, 6H), 2.02 (s, 3H), 1.93 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 170.1, 41.3, 39.7, 38.0, 35.6, 22.8. MS *m/e* 163 ($M+H_2O$). Anal. Calcd. for $C_6H_{15}N_3O \cdot H_2O$: C,44.17; H,10.43; N,25.77. Found: C,44.36; H,10.44; N,25.83.

N-Acetyl-3,6-diazaoctane-1,8-diamine (2b):

2b is an oily liquid. TLC (A) R_f = 0.29; mp=111-112° C; IR (film) 1659, 1576 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.34 (q, 2H), 2.80 (t, 2H), 2.40-2.51 (m, 8H), 1.99 (s, 3H), 1.74 (s, 4H); ^{13}C NMR ($CDCl_3$) δ 170.2, 40.9, 39.5, 38.4, 35.8, 23.0. MS *m/e* 224 ($M+2H_2O$). Anal. Calcd. for $C_8H_{20}N_4O \cdot 2H_2O$: C,42.86; H,10.71; N,25.00. Found: C,43.21; H,10.64; N,25.23.

N,N'-Diacetyl-3-azapentane-1,5-diamine (2c):

2c is a white solid. TLC (A) R_f = 0.69; n_D^{20}=1.4974; IR (film) 1661, 1577 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.33 (q, 4H), 2.77 (t,

4H), 2.01 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 170.7, 39.3, 36.2, 22.9. MS *m/e* 205 ($M+H_2O$). Anal. Calcd. for $C_8H_{17}N_3O_2 \cdot H_2O$: C,46.83; H,9.27; N,20.49. Found: C,47.01; H,9.30; N,20.58.

N,N'-Diacetyl-3,6-diazaoctane-1,8-diamine (2d):

TLC (A) R_f = 0.54; mp=150-152°C; IR (film) 1660, 1576 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.24-3.40 (m, 4H), 2.46-2.57 (m, 8H), 2.19 (br.s, 2H), 2.01 (s, 3H), 1.99 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 170.2, 39.2, 38.5, 35.8, 23.0. MS *m/e* 248 ($M+H_2O$). Anal. Calcd for $C_{10}H_{22}N_4O_2 \cdot H_2O$: C,48.39; H,9.68; N,22.58. Found: C,48.63; H,9.66; N,22.69.

General Procedure for the Preparation of Carboxymethyl Ethyl Esters of Acetylated Polyamines (3).

Depending on the starting material, the molar equivalent of ethylbromoacetate used in the reaction was 6 for **2a** and 8 for **2b**, respectively. Ethylbromoacetate (8.9 g,53.4 mmol) was added dropwise at room temperature to the stirred mixture of **2a** (1.29 g, 8.9 mmol) or **2b** (1.25 g, 6.7 mmol, triethylamine (5.39 g, 53.4mmol), toluene (20 ml) and chloroform (20 ml). Stirring was continued for 24 hours at room temperature. Then the solvents were evaporated under reduced pressure. The remaining residue was dissolved in chloroform, washed with water and dried over sodium sulfate. Solvent was removed in vacuo and the product was purified by flash chromatography over silica gel (solvents: chloroform then B or acetone then C).

The structures of this application example were confirmed by the same procedure as used for **2a-2d.** In the NMR spectrum, the two equivalent methylene groups bound with the same nitrogen atom appeared as a four-proton singlet at 3.6 ppm. The other methylene groups are two-proton singlets between 3.4 and 3.5 ppm.

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