ACID-CATALYSED MIGRATION OF N^4-ACYL GROUPS IN CYTOSINE DERIVATIVES

Antonín HOLÝ

Institute of Organic Chemistry and Biochemistry, Czechoslovak Academy of Sciences, 166 10 Prague 6

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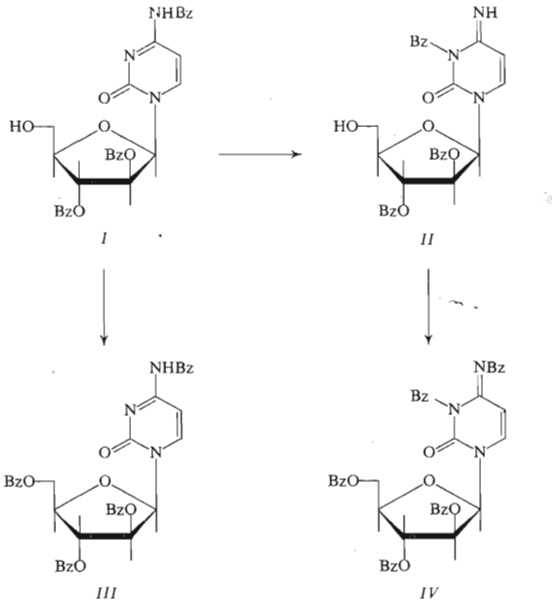
Heating 1-(2,3-di-O-benzoyl-β-D-arabinofuranosyl)-N^4-benzoylcytosine (*I*) in 80% acetic acid afforded 1-(2,3-di-O-benzoyl-β-D-arabinofuranosyl)-N^3-benzoylcytosine (*II*). Benzoylation of 5'-O-tritylcytidine (*V*) led to the 2',3',N^4-tribenzoyl derivative *VI* which was refluxed with 80% acetic acid to give 2',3',N^3-tribenzoylcytidine (*VII*). Analogously, 2',3',5',N^4-tetrabenzoylcytidine (*IX*), prepared by benzoylation of cytidine with benzoyl cyanide, gave on reflux with 80% acetic acid 2',3',5',N^3-tetrabenzoylcytidine (*X*). Under identical conditions, 1-methyl-N^4-benzoylcytosine (*XI*) afforded directly 1-methyluracil (*XII*). This migration takes place also in acetyl derivatives of cytosine nucleosides: 2',3',5',N^4-tetraacetylcytidine (*XIII*) was transformed to the N^3-acetylcytosine derivative *XIV*. On the other hand, migration of acetyl or benzoyl group from the exo-amino group of adenine has not been observed under the mentioned conditions. The migration of the N^4-acyl group of cytosine derivatives proceeds best in aqueous acetic acid, more slowly also in anhydrous acetic acid, but not by action of trifluoroacetic acid in 1,2-dichloroethane.

In one of our previous communications[1] we described the unexpected formation of isomeric tribenzoyl derivatives of 1-(β-D-arabinofuranosyl)cytosine during hydrolysis of 5'-O-trityl-2',3',N^4-tribenzoyl-1-(β-D-arabinofuranosyl)cytosine with 80% acetic acid. The ^{1}H-NMR study has shown that, in addition to the expected product *I*, the reaction afforded also a substantial amount of the isomeric derivative *II* which contained the unusual N^3-benzoylcytosine grouping. The structure of this compound was confirmed also by its methanolysis, leading to uridine as the sole product. Since this reaction is very interesting we tried to answer the question whether the compound *II* is formed from the N^3-benzoyl derivative already present in the starting trityl compound (which would mean the very improbable N^3-benzoylation of the cytosine nucleus) or from the N^4-benzoylcytosine derivative *I* by benzoyl migration under conditions required for the acid-catalysed removal of the protecting trityl group.

Since methanolysis of N^3-benzoylcytosine derivatives must lead to uracil derivatives[1], the first alternative was excluded by using the reverse reaction sequence. The starting 5'-O-trityl-2',3',N^4-tribenzoyl-1-(β-D-arabinofuranosyl)cytosine was first debenzoylated by methanolysis to give the 5'-O-trityl derivative which on hydrolysis

with 80% acetic acid was transformed to araC, identified by paper chromatography and UV absorption spectrum at low pH. On the other hand, it was found that refluxing the compound *I* in 80% acetic acid gave quantitatively the isomer *II* whereas the latter compound did not change under these conditions. Besides by the above-mentioned techniques[1], the structure of compounds *I* and *II* was proved also by their transformation to perbenzoyl derivatives; whereas the compound *I* on treatment with benzoyl chloride in pyridine afforded the 2',3',5',N^4-tetrabenzoyl derivative *III*, identical with the product obtained by direct benzoylation of araC, the isomer *II* under identical conditions gave the pentabenzoyl derivative *IV*. Since the compound *IV* was unusually insoluble, it was not possible to prove its structure directly by ^{1}H-NMR or IR spectra; its methanolysis, however, afforded 1-(β-D-arabinofuranosyl)-uracil as the sole product (Scheme 1):



In formulae *I*–*IV*, Bz = benzoyl residue

SCHEME 1

In formulae *V* – *X*, Tr = trityl, Bz = benzoyl group

SCHEME 2

Analogously, 5'-O-tritylcytidine (*V*) (ref.[2]) was transformed to 2',3',N^4-tribenzoyl derivative *VI* which on reflux with 80% acetic acid afforded finally 2',3',N^3-tribenzoylcytidine (*VII*). The structure of *VII* was proved by ^{1}H-NMR spectroscopy, as well as by its methanolysis to uridine as the sole product.

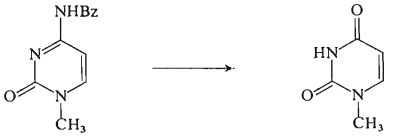
Cytidine (*VIII*) was transformed to its 2',3',5',N^4-tetrabenzoate *IX* by reaction with benzoyl cyanide[3]. The compound *IX* (which on methanolysis was transformed back to cytidine) under analogous conditions (boiling 80% acetic acid) gave 2',3',5',N^3-tetrabenzoylcytidine (*X*) in quantitative yield. Also in this case, the final structural proof, besides the NMR-spectrum, was the unequivocal methanolysis to uridine. This reaction proceeds best in boiling 80% acetic acid, but it takes place slowly also at room temperature. The migration rate is slower in 100% acetic acid and no reaction was observed in the presence of trifluoroacetic acid in 1,2-dichloroethane at room temperature.

The benzoyl migration is not restricted only to nucleoside derivative of cytosine: 1-methyl-N^4-benzoylcytosine (*XI*), prepared by benzoylation of 1-methylcytosine[4], reacted also in boiling 80% acetic acid; in this case, however, the reaction product was 1-methyluracil (*XII*). Obviously, the probable migration product is labile and undergoes a subsequent hydrolysis. The properties of the obtained compound *XII* corresponded entirely to those of an authentic material, including its characteristic UV spectrum[5].

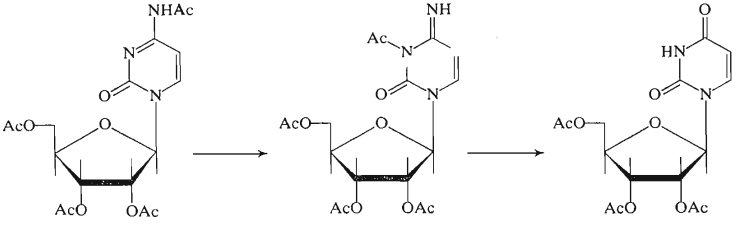
The N^4-acetyl group is also not stable under the reaction conditions employed: 2',3',5',N^4-tetraacetylcytidine (*XIII*) in boiling 80% acetic acid afforded a mixture from which we isolated 2',3',5'-tri-O-acetylcytidine, together with 2',3',5',N^3-tetraacetylcytidine (*XIV*) (which on methanolysis again afforded uridine), and obviously also 2',3',5'-tri-O-acetyluridine (*XV*) (as the product of hydrolysis of *XIV*).

The acetyl and benzoyl migrations are apparently restricted to the N^4-acyl derivatives of 1-substituted cytosines. The comparison experiments with 2',3',5',N^6-tetrabenzoyladenosine (*XVI*) were negative whereas in 2',3',5',N^6-tetraacetyladenosine (*XVII*) the N-acetyl group was solely hydrolysed under formation of 2',3',5'-tri-O-acetyladenosine (*XVIII*). Invariably, no inosine derivatives were detected in the reaction mixtures.

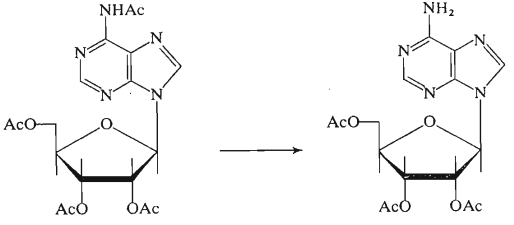
Although the N^4-acyl migration in the cytosine derivatives takes place even under anhydrous conditions, its rate increases significantly in the presence of water. From the preparative point of view it is necessary to keep this reaction in mind when choosing protecting groups in cytosine nucleosides which can be removed under acidic conditions. The loss of cytosine derivatives in removing *e.g.* a trityl group can be substantial and it is necessary to use either more labile groups (substituted trityl groups) or to perform the cleavage with a strong acid in an anhydrous medium at low temperature. From this point of view it is necessary to reevaluate some older investigations describing syntheses of protected cytosine nucleosides prepared *via* the trityl derivatives.



XI *XII*



XIII *XIV* *XV*



XVII *XVIII*

In formulae *XI*–*XVIII*, Ac = acetyl, Bz = benzoyl group

SCHEME 3

EXPERIMENTAL

The melting points were determined on a Kofler block and are uncorrected. Unless stated otherwise, the solutions were taken down at 40°C/15 Torr and the compounds were dried over phosphorus pentoxide at 0·1 Torr.

Thin-layer chromatography on silica gel was performed on Silufol UV_{254} plates in chloroform (system S1), chloroform–ethanol 95 : 5 (S2), or chloroform–ethanol 9 : 1 (S3). Paper electrophoresis was carried out on paper Whatman No 3 MM in 0·05M triethylammonium borate, pH 7·5 at 20 V/cm, time 90 min. The absorption spectra were measured on a Specord spectrometer (Carl Zeiss, Jena) in methanol or 0·01M-HCl, ^{1}H-NMR spectra on a Varian 100 instrument in deuteriochloroform with hexamethyldisiloxane as internal standard (the chemical shifts are expressed in ppm, the coupling constants in Hz).

1-(2,3,5-Tri-O-benzoyl-β-D-arabinofuranosyl)-N^4-benzoylcytosine (*III*)

a) By benzoylation of 1-(β-D-*arabinofuranosyl*)*cytosine.* Benzoyl chloride (1·2 ml; 10·3 mmol) was added dropwise to a stirred solution of 1-(β-D-arabinofuranosyl)cytosine (0·34 g; 1·4 mmol) in pyridine (10 ml). After stirring at room temperature overnight, ethanol (5 ml) was added and after 1 h the mixture was taken down *in vacuo*. The residue was diluted with chloroform (50 ml), extracted with water (3 . 20 ml), the chloroform solution dried over magnesium sulfate, filtered and taken down *in vacuo*. The residue was subjected to chromatography on one plate (35 × 20 × × 0·3 cm) of silica gel, containing a fluorescent indicator (made in the Service Laboratories of this Institute), in the system S1. The product band was eluted with methanol and the residue crystallised from an ethanol–light petroleum mixture, yielding 0·70 g (76%) of the compound *III*, m.p. 155°C. For $C_{37}H_{19}N_3O_9$ (659·6) calculated: 67·36% C, 4·43% H, 6·37% N; found: 67·82% C, 4·39% H, 6·52% N. R_F 0·55 (S1). ^{1}H-NMR spectrum: 4·68 (m, 1 H) $H_{4'}$; 4·78 (br s, 2 H) 2 $H_{5'}$; 5·68 (m, 1 H) $H_{3'}$; 5·94 (dd, 1 H, $J_{2',1'} = 4·5$, $J_{2',3'} = 1·5$) $H_{2'}$; 6·49 (d, 1 H, $J_{1',2'} = 4·5$) $H_{1'}$; 7·20—7·63 (m, 11 H) aromatic protons + H_5 + H_6 + NH, 7·65—8·25 (m, 12 H) aromatic protons.

b) *By benzoylation of* 1-(2,3-O-*benzoyl*-β-D-*arabinofuranosyl*)-N^4-*benzoylcytosine* (I). Triethylamine (0·2 ml) was added to a solution of the compound *I* (see ref.[1]; 0·56 g; 1 mmol) and benzoyl cyanide (0·20 g; 1·52 mmol) in acetonitrile (10 ml). After standing for 2 h at room temperature the mixture was taken down, the residue coevaporated with ethanol and crystallised from ethanol–light petroleum, yielding 0·50 g (76%) of *III*, m.p. 155°C, no depression on admixture with the compound prepared under *a*); R_F 0·55 (S1), Methanolysis with 0·1M sodium methoxide in methanol, followed by electrophoresis of the mixture, afforded a single product, λ_{max} 281 nm (0·01N--HCl).

1-(2,3,5-Tri-O-benzoyl-β-D-arabinofuranosyl)-N^3,N^4-dibenzoylcytosine (*IV*)

Benzoyl chloride (1 ml) was added dropwise to a stirred solution of the compound *II* (ref.[1]; 1·0 g; 1·8 mmol) in pyridine (10 ml) and the mixture set aside at room temperature overnight. Ethanol (1 ml) was added and after standing for 2 h at room temperature the mixture was taken down *in vacuo*. The residue was diluted with chloroform (100 ml), the solution washed with water (2 . 50 ml), dried over magnesium sulfate, filtered, taken down *in vacuo* and the remaining material boiled with ethanol (100 ml) for 5 min. After cooling, the product was collected on filter, washed with ethanol and ether and dried; yield 1·1 g (79·5%) of compound *IV* which did not melt below 260°C. For $C_{44}H_{33}N_3O_{10}$ (763·7) calculated: 69·18% C, 4·35% H, 5·50% N; found: 69·05% C, 4·52% H, 5·67% N. Methanolysis with 0·1M sodium methoxide at room temperature

overnight, and subsequent isolation by paper electrophoresis afforded uracil arabinoside as the sole product (UV: λ_{max} 262 nm).

5′-O-Trityl-2′,3′,N^4-tribenzoylcytidine (*VI*)

Benzoyl chloride (4·5 ml; 38·8 mmol) was added dropwise to a stirred solution of 5′-O-tritylcytidine (*V*; ref.[2]) (5·0 g; 10·3 mmol) in pyridine (30 ml) and the mixture was set aside at room temperature overnight. Ethanol (5 ml) was added, followed after 30 min by ethyl acetate (100 ml). After washing with water (3 . 100 ml) the solvent was evaporated, the residue codistilled with toluene (3 . 100 ml) *in vacuo* and then chromatographed on silica gel (according to Pitra; 30—60 mesh, 200 g) in chloroform. The product-containing fractions were combined and dried *in vacuo*, yielding 3·5 g (42·5%) of compound *VI* as an amorphous foam, R_F 0·28 (S2). For $C_{49}H_{39}N_3O_8$ (797·8) calculated: 73·76% C, 4·93% H, 5·27% N; found: 73·48% C, 4·78% H, 5·43% N. A solution of *VI* (0·30 g) in 30% methanolic ammonia (10 ml) on standing overnight at room temperature afforded 5′-O-tritylcytidine (*V*) as the only product (R_F 0·10 in S3).

2′,3′,N^3-Tribenzoylcytidine (*VII*)

A solution of the compound *VI* (1·6 g; 2 mmol) in 80% acetic acid (15 ml) was refluxed for 45 min, taken down *in vacuo*, codistilled with toluene (3 . 10 ml) and the residue chromatographed on one plate of silica gel (*vide supra*) in the system S2. The product was obtained by elution with methanol (300 ml), evaporation and crystallisation from ethanol with addition of light petroleum until the solution became turbid; yield 0·78 g (70%) of compound *VII*, m.p. 192°C. For $C_{30}H_{25}N_3O_7$ (555·5) calculated: 64·86% C, 4·53% H, 7·56% N; found: 64·43% C, 5·12% H, 7·26% N. R_F 0·18 (S2). ^{1}H-NMR spectrum 3·80 (m, 2 H) 2 H_5, 4·38 (m, 1 H), 6·15—6·50 (m, 3 H) H_2' + H_3' + H_5, 6·34 (d, 1 H, J = 6·0) $H_{1'}$, 7·15—8·15 (m, 16 H) aromatic protons + H_6, 11·2 (br s, 1 H) NH. Methanolysis with 0·1M sodium methoxide at room temperature overnight, followed by electrophoretic isolation, afforded uridine as the sole product (identified by its electrophoretic mobility and λ_{max} 262 nm).

2′,3′,5′,N^4-Tetrabenzoylcytidine (*IX*)

Triethylamine (2 ml) was added to a stirred mixture of cytidine (2·43 g; 10 mmol), benzoyl cyanide (6·5 g; 49·5 mmol) and acetonitrile (50 ml) and the stirring was continued for 1 h. The separated product was filtered, washed with acetonitrile, ethanol, ether and dried *in vacuo*, affording 4·3 g (65%) of the compound *IX*, m.p. 206°C. R_F 0·55 (S2); $[\alpha]_{20}^{D}$ −50·8° (*c* 0·5, dimethylformamide). For $C_{37}H_{29}N_3O_9$ (659·6) calculated: 67·37% C, 4·42% H, 6·37% N; found: 67·22% C, 4·39% H, 6·73% N. ^{1}H-NMR spectrum: 4·60—5·0 (complex m, 3 H) $H_{4'}$ + 2 $H_{5'}$, 6·02 (complex m, 2 H) $H_{2'}$ + $H_{3'}$, 6·24 (s, 1 H) $H_{1'}$, 7·25—7·70 + 7·80—8·10 (2 m, 21 H) aromatic protons + H_5, 8·21 (d, 1 H) H_6, 11·32 (br s, 1 H) NH. Methanolysis with 0·1M sodium methoxide at room temperature overnight and subsequent isolation by electrophoresis afforded cytidine as the sole product (according to the electrophoresis and λ_{max} 280 nm at pH 2).

2′,3′,5′,N^3-Tetrabenzoylcytidine (*X*)

A solution of the compound *IX* (2·4 g; 3·64 mmol) in 80% acetic acid (40 ml) was refluxed for 1 h, taken down and coevaporated with ethanol (3 . 20 ml). The residue was chromatographed on two plates of silica gel (*vide supra*) in the system S2 and the product bands were eluted with methanol (500 ml). The conversion of *IX* was quantitative. The solvent was evaporated and the residue dried *in vacuo*, yielding 1·72 g (72%) of compound *X* as an amorphous foam, R_F 0·20 (S2). For

$C_{37}H_{29}N_3O_9$ (659·6) calculated: 67·36% C, 4·43% H, 6·37% N; found: 67·13% C, 4·21% H, 6·10% N. ^{1}H-NMR spectrum: 4·50—5·0 (m, 3 H) $H_{4'} + 2\,H_{5'}$, 5·60 (d, 1 H, $J = 8·0$) H_5, 5·91 (m, 1 H, $J_{3',2'} = 6·0$, $J_{3',4'} = 4·0$) $H_{3'}$, 5·75 (dd, 1 H, $J_{1',2'} = 5·0$, $J_{2',3'} = 6·0$) $H_{2'}$, 6·31 (d, 1 H, $J_{1',2'} = 5·0$) $H_{1'}$, 7·20—7·60 + 7·80—8·20 (2 m, 20 H) aromatic protons, 7·40 (d, 1 H, $J = 8·0$) H_6, 9·31 (br s, 1 H) NH. Methanolysis with 0·1M sodium methoxide at room temperature overnight and subsequent electrophoresis gave uridine as the only product ($E_{Urd} = 1$, λ_{max} 262 nm at pH 2).

Treatment of Compound *IX* with Acid

a) With acetic acid: A solution of the compound *IX* (0·33 g; 0·5 mmol) in acetic acid (20 ml) was refluxed for 16 h (calcium chloride protective tube). The reaction mixture was taken down *in vacuo* and the residue set aside overnight with 0·2M sodium methoxide in methanol (10 ml). A part (2 ml) of the mixture was chromatographed on a sheet of Whatman No 3 MM paper in the system 2-propanol-conc. ammonia-water (7 : 1 : 2) and the product eluted. The UV absorption measurements at 250, 280 and 290 nm in 0·01N hydrochloric acid showed that the product contained 22% of uridine and 78% of cytidine.

b) With trifluoroacetic acid: A solution of the compound *IX* (0·33 g; 0·5 mmol) in 1,2-dichloroethane (20 ml) and trifluoroacetic acid (0·20 ml) was stirred at room temperature for 24 h and neutralised with triethylamine. The mixture was taken down and the residue shown (S2) to be the unchanged compound *IX* (analysed in the same manner as described in the preceding experiment). According to the spectrophotometric measurement the mixture contained only cytidine.

N^4-Benzoyl-1-methylcytosine (*XI*)

Benzoyl chloride (1·8 ml; 15·5 mmol) was added dropwise to a stirred suspension of 1-methylcytosine[5] (1·3 g; 10·4 mmol) in pyridine (15 ml) and the stirring was continued at room temperature overnight. Ethanol (5 ml) was added and after 30 minutes standing the mixture was poured in water (100 ml). The product was taken up in chloroform (3 . 25 ml), the extract washed with water (3 . 20 ml), dried over magnesium sulfate and taken down. The residue was crystallised from ethanol, affording 1·70 g (71·5%) of compound *XI*, m.p. 215°C. For $C_{12}H_{11}N_3O_2$ (229·2) calculated: 62·87% C, 4·84% H, 18·33% N; found: 63·01% C, 5·29% H, 17·86% N. R_F 0·70 (S3).

1-Methyluracil (*XII*)

A solution of the compound *XI* (1·15 g; 5 mmol) in 80% acetic acid (25 ml) was refluxed for 5 h, taken down and the residue coevaporated with ethanol (3 . 50 ml). Crystallisation from ethanol yielded 0·50 g (79·5%) of compound *XII*, m.p. 230—231°C. R_F 0·48 (S3). For $C_5H_6N_2O_2$ (126·1) calculated: 47·61% C, 4·79% H, 22·21% N; found: 47·94% C, 4·68% H, 21·99% N. UV-spectrum: λ_{max} 266 nm, λ_{max} 235 nm (pH 2).

2′,3′,5′,N^4-Tetraacetylcytidine (*XIII*)

A mixture of cytidine (1 g; 4·1 mmol), acetic anhydride (40 ml) and 4-dimethylaminopyridine (0·3 g) was stirred until it became homogeneous and then set aside overnight. After evaporation at 40°C/0·1 Torr, the residue was codistilled with toluene (2 . 25 ml) under the same conditions. A solution of the residue in chloroform (100 ml) was washed with water (20 ml), dried over magnesium sulfate, filtered and taken down *in vacuo*. The remaining product was dried at 0·1 Torr, yielding 1·70 g (100%) of the chromatographically pure *XIII*; R_F 0·63 (S3). ^{1}H-NMR spectrum:

2·08 (s, 6 H) + 2·13 (s, 3 H) + 2·25 (s, 3 H) acetyl, 4·22–4·60 (m, 3 H) $H_{4'}$ + 2 $H_{5'}$, 5·48 (t, 1 H, $J_{1',2'} = J_{2',3'} = 3·5$) $H_{2'}$, 6·10 (d, 1 H, $J_{1',2'} = 3·5$) $H_{1'}$, 7·51 (d, 1 H, $J = 8·0$) H_6, 7·98 (d, 1 H, $J = 8·0$), H_5, 9·70 (s, 1 H) NH. UV-spectrum (ethanol): λ_{max} 250 nm, 302 nm, λ_{min} 228 nm, 278 nm.

Reaction of Compound *XIII* with 80% Acetic Acid

A mixture of the compound *XIII* (1 g; 2·43 mmol) and 80% acetic acid (25 ml) was refluxed for 4 h and then taken to dryness. The residue was codistilled with ethanol (2 . 20 ml) and chromatographed on one plate of silica gel (*vide supra*) in the system S2. The product bands were eluted with ethyl acetate, the eluates taken down and the residues dried *in vacuo*. Following products were obtained: a compound (0·10 g) of R_F 0·05 (S3), λ_{max} 242, 270 nm in ethanol, which after methanolysis afforded a product with λ_{max} 281 nm (pH 2) confirming thus the cytidine structure; a compound (0·20 g) of R_F 0·15 (S3), λ_{max} 242, 270 nm (ethanol) (after methanolysis: λ_{max} 281 nm (pH 2)); a compound (0·10 g) of R_F 0·30 (S3), λ_{max} 260 nm (ethanol) (after methanolysis: λ_{max} 262 nm (pH 2); a uridine derivative); a compound (0·10 g) of R_F 0·35 (S3), λ_{max} 260 nm (ethanol) (after methanolysis: λ_{max} 262 nm, corresponds to 2′,3′,5′-tri-O-acetyluridine); and finally compound *XIV* of R_F 0·50 (0·40 g; 40%), λ_{max} 260 nm (ethanol); for $C_{17}H_{21}.N_3O_9$ (411·4) calculated: 49·63% C, 5·15% H, 10·22% N; found: 48·26% C, 4·85% H, 10·35% N. ^{1}H-NMR spectrum: 2·06 (s, 3 H) + 2·10 (s, 9 H) acetyl, 4·35 (m, 3 H) $H_{4'}$ + 2 $H_{5'}$, 5·36 (m, 2 H) $H_{2'}$ + $H_{3'}$, 5·80 (d, 1 H, $J = 8·0$) H_5, 6·0 (m, 1 H, virt. coupling) $H_{1'}$, 7·80–9·20 (br s, 1 H) NH. Its methanolysis led to uridine as the only product ($E_{Urd} = 1$, λ_{max} 262 nm at pH 2).

Reaction of 2′,3′,5′,N^6-Tetraacetyladenosine with 80% Acetic Acid

A solution of the compound *XVI* (ref.[6]) (1·0 g; 2·3 mmol) in 80% acetic acid (40 ml) was refluxed for 3 h. After 1 h the reaction was complete and the mixture was taken down *in vacuo*. The residue was codistilled with ethanol (3 . 20 ml) and chromatographed on one plate of silica gel (*vide supra*) in the system S3. The product was eluted with methanol (300 ml), the eluate taken down and the residue crystallised from ethanol, yielding 0·60 g (66·2%) of the compound *XVIII*, m.p. 174°C. For $C_{16}H_{19}N_5O_7$ (393·4) calculated: 48·85% C, 4·87% H, 17·81% N; found: 48·58%C 4·78% H, 18·43% N. R_F 0·40 (S3). This product was identical with an authentic sample of *XVIII*. Its methanolysis afforded as the sole product adenosine, whose identity with an authentic material was proved by electrophoresis, paper chromatography in the system 2-propanol–conc. ammonia–water (7 : 1 : 2), and UV spectra (λ_{max} 258 nm at pH 2).

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