Aminocyclitols. XXVI. A Synthesis of Aminocyclopentanetetrols

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Hydrogenation of 2,3-*O*-cyclohexylidene-5-nitro-1,2,3,4-cyclopentanetetrol, subsequently followed by hydrolysis and acetylation, afforded (1,4/2,3,5)- and DL-(1,2,3/4,5)-5-acetamido-1,2,3,4-tetra-*O*-acetyl-1,2,3,4-cyclopentanetetrol (**3** and **14**). Beginning with (1,4/2,3,5)-5-acetamido-1,4-di-*O*-acetyl-2,3-*O*-cyclohexylidene-1,2,3,4-cyclopentanetetrol (**2**), two hitherto unknown (1,2,3,4,5)- and DL-(1/2,3,4,5)-5-acetamido-1,2,3,4-tetra-*O*-acetyl-1,2,3,4-cyclopentanetetrol (**10** and **12**) were prepared. The structures were established by proton magnetic resonance spectra.

Six DL-pairs and four meso compounds are theoretically possible in aminocyclopentanetetrols and nowadays three DL-pairs and two meso compounds are known.[1,2]

A presence of five membered carbocyclic compounds in antibiotics aristeromycin[3,4] and pactamycin[5,6] has stimulated the authors to explore a synthesis of new aminocyclopentanetetrols. In 1965, Angyal and Gero[7] prepared 2,3-*O*-cyclohexylidene-5-nitro-1,2,3,4-cyclopentanetetrol (**1**) by cyclization of *cis*-3,4-cyclohexylidenedioxy-2,5-dihydroxytetrahydrofuran with nitromethane. Very recently, it has been described that two aminocyclopentanetetrols were obtained as their pentaacetyl-derivatives by catalytic hydrogenation of **1**.[2]

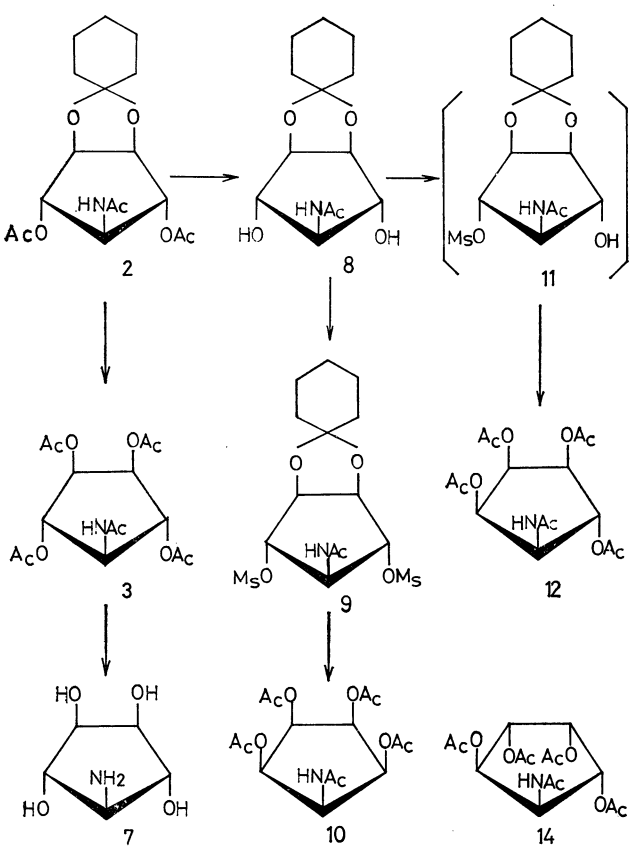
In the present article, the authors wish to report a preparation of four aminocyclopentanetetrols in which a DL-pair and a meso compound are hitherto unknown ones.

Catalytic hydrogenation of **1** in ethanol with Raney nickel T-4,[8] followed by acetylation afforded (1,4/2,3,5)-5-acetamido-1,4-di-*O*-acetyl-2,3-*O*-cyclohexylidene-1,2,3,4-cyclopentanetetrol (**2**)[2] in 40% yield. Hydrolysis of **2** in 80% aqueous acetic acid and subsequent acetylation of the hydrolyzate yielded (1,4/2,3,5)-5-acetamido-1,2,3,4-tetra-*O*-acetyl-1,2,3,4-cyclopentanetetrol (**3**)[1,2] of mp 147.5°C in 89% yield.

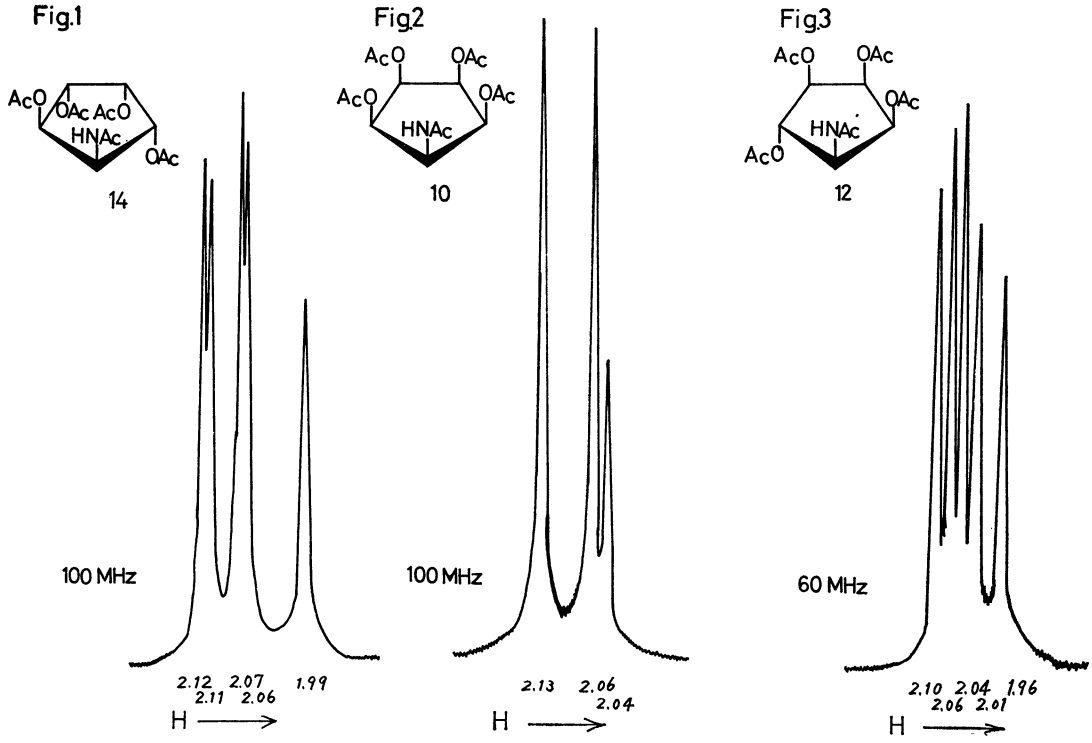
From the hydrogenation mixture, it was successfully attempted to isolate another isomer by a following procedure. The mother liquor from which the compound **2** had been obtained was settled in a refrigerator to give DL-(1,2,3/4,5)-5-acetamido-1,4-di-*O*-acetyl-2,3-*O*-cyclohexylidene-1,2,3,4-cyclopentanetetrol (**13**). Hydrolysis of **13** in 80% aqueous acetic acid, followed by acetylation, gave DL-(1,2,3/4,5)-5-acetamido-1,2,3,4-tetra-*O*-acetyl-1,2,3,4-cyclopentanetetrol (**14**).[1]

Beginning with the compound **2**, two unknown aminocyclopentanetetrols were prepared by the following reactions. When **2** was treated with ammonia in methanol, *O*-acetyl groups were selectively removed to give 5-acetamido-2,3-*O*-cyclohexylidene-1,2,3,4-cyclopentanetetrol (**8**) of mp 160.5°C in 61% yield. Methanesulfonylation of **8** with a large excess amount of methanesulfonyl chloride in pyridine afforded 1,4-di-*O*-methane sulfonyl derivative (**9**) in 69% yield. A treatment in boiling water and subsequent acetylation converted **9** to (1,2,3,4,5)-5-acetamido-1,2,3,4-tetra-*O*-acetyl-1,2,3,4-cyclopentanetetrol (**10**) of mp 173°C in a yield of 62%. The compound **10** showed a remarkable depression of the melting point, when it was mixed with (1,4,5/2,3)-5-acetamido-1,2,3,4-tetra-*O*-acetyl-1,2,3,4-cyclopentanetetrol of mp 176.5°C.[2]

A similar treatment of **8** with the smaller amount of methanesulfonyl chloride yielded a mixture of mono-*O*-methanesulfonyl derivative (**11**) and **9**. The mixture was heated in boiling water and subsequently acetylated to give a mixture of DL-(1/2,3,4,5)-5-acetamido-1,2,3,4-tetra-*O*-acetyl-1,2,3,4-cyclopentan-



1) A. Hasegawa and H. Z. Sable, *J. Org. Chem.*, **31**, 4154 (1966).
2) R. Ahluwalia, S. J. Angyal, and B. M. Luttrell, *Aust. J. Chem.*, **23**, 1819 (1970).
3) T. Kishi, M. Muroi, T. Kusaka, M. Nishikawa, K. Kamiya, and K. Mizuno, *Chem. Commun.*, **1967**, 852.
4) T. Kusaka, H. Yamamoto, M. Shibata, M. Muroi, T. Kishi, and K. Mizuno, *J. Antibiotics (Tokyo), Ser. A*, **21**, 255 (1968).
5) A. D. Argoudelis, H. K. Jahnke, and J. A. Fox, *Antimicrobial Agents & Chemotherapy*, 191 (1961).
6) P. F. Wiley, H. K. Jahnke, F. McKellar, R. B. Kelly, and A. D. Argoudelis, *J. Org. Chem.*, **35**, 1420 (1970).
7) S. J. Angyal and S. D. Gero, *Aust. J. Chem.*, **18**, 1973 (1965).
8) S. Nishimura, This Bulletin, **32**, 61 (1959).



etetrol (**12**) of mp 116°C and the compound **10**, which were separated by a chromatographic fractionation.

The compound **3** (mp 147.5°C) was identical with the compound described by Hasegawa and Sable[1] and by Ahluwalia, Angyal, and Luttrell.[2] The proton magnetic resonance (PMR) spectrum of **3** revealed three sharp signals at δ 1.95, 2.05 and 2.08 (3 : 6 : 6 protons) which were attributed to an acetamido, two acetoxy (on C-2 and C-3) and two acetoxy groups (on C-1 and C-4) respectively.

The compound **13** showed three sharp signals in its PMR spectrum for an acetamido and two acetoxy groups at δ 1.96, 2.10 and 2.12 (3 : 3 : 3 protons), proving that the two acetoxy groups on C-1 and C-4 had different configurations for the acetamido group. And the compound **14** (mp 188.5°C) showed five sharp signals in its PMR spectrum at δ 1.99, 2.06, 2.07, 2.11 and 2.12 (3 : 3 : 3 : 3 : 3 protons) indicating that this compound was not symmetrical and identical with DL-(1,2,3/4,5)-5-acetamido-1,2,3,4-tetra-*O*-acetyl-1,2,3,4-cyclopentanetetrol described by Hasegawa and Sable.[1]

The compound **10** (mp 173°C) showed three sharp signals at δ 2.04, 2.06 and 2.13 (3 : 6 : 6 protons) in its spectrum, showing that **10** had a symmetrical molecular structure.

Among four theoretically possible meso compounds, two isomers of (1,2,3,4,5) and (1,2,3,4/5) have never been described and the compound **10** should be one of these two isomers.

The following reaction mechanism was proposed for the reaction from **9** to **10**. Removal of a methanesulfonyloxy group yields an oxazolinium ion with a participation of a neighboring *trans*-acetamido group and the cyclic carbonium ion is attacked by water to give *cis*-acetamido alcohol.[9,10] The same anchimeric reaction occurs again with another methanesulfonyloxy group to give the (1,2,3,4,5)-isomer.

The compound **12** (mp 116°C) exhibited five sharp signals in its spectrum at δ 1.96, 2.01, 2.04, 2.06 and 2.10 (3 : 3 : 3 : 3 : 3 protons) indicating that this compound was an unsymmetrical one. Therefore, it was reasonably established that **12** was DL-(1/2,3,4,5)-isomer. The above mentioned reaction mechanism is also proposed in this reaction.

Now seven isomers of aminocyclopentanetetrols have been described in their pentaacetyl derivatives and only three isomers remain unknown. An attempt to synthesize these isomers is still under way.

Experimental

A melting point was determined in a liquid bath and was uncorrected. PMR spectrum was recorded on a Varian A-60D spectrometer, unless otherwise noted, at a frequency of 60 MHz in deuteriochloroform with tetramethylsilane as an internal standard. The peak position was expressed in δ-value.

2,3-O-Cyclohexylidene-5-nitro-1,2,3,4-cyclopentanetetrol (**1**). A mixture of *cis*-3,4-cyclohexylidenedioxytetrahydrofuran-2,5-diol (10.4 g) and nitromethane (2.8 g) was treated with sodium methoxide by the method of Angyal and Gero[7] to give 8.1 g (65%) of **1** as an oily product. The product was used for a successive reaction without any purification.

(1,4/2,3,5)-5-Acetamido-1,4-di-O-acetyl-2,3-O-cyclohexylidene-1,2,3,4-cyclopentanetetrol (**2**). A 5.4 g portion of **1** was hydrogenated in ethanol (50 m*l*) with Raney nickel T-4

9) E. S. Gould, "Mechanism and Structure in Organic Chemistry," Holt, Rinehart and Winston, New York (1959), p. 566.
10) T. Suami and S. Ogawa, This Bulletin, **37**, 194 (1964).

catalyst[8] at 3.4 kg/cm² of hydrogen stream for 20 hr. After the catalyst was removed by filtration, the ethanol solution was evaporated under reduced pressure to give 4.7 g of a residual oil. The residue was acetylated in a mixture of acetic anhydride (20 ml) and pyridine (20 ml). The mixture was evaporated *in vacuo* and the residue was crystallized in benzene to give 3.2 g (45%) of needles, mp 137—139°C. Recrystallization from benzene gave 2.9 g (40%) of crystals, mp 140.5—141.5°C. PMR: δ 1.93 (3 protons, NAc) and 2.08 (6 protons, OAc×2). (Found: C, 57.33; H, 6.93; N, 3.77%).

(1,4/2,3,5)-5-Acetamido-1,2,3,4-tetra-O-acetyl-1,2,3,4-cyclopentanetetrol (**3**). A 1.33 g portion of **2** was heated under reflux for 4 hr in 80% aqueous acetic acid (20 ml) and the mixture was evaporated *in vacuo*. The residue was acetylated with acetic anhydride in pyridine to give 1.10 g (89%) of the crude product. Recrystallization from ether afforded needle crystals of mp 146.5—147.5°C. PMR: δ 1.95 (3 protons, NAc), 2.05 (6 protons, OAc×2, on C-2 and C-3), 2.08 (6 protons, OAc×2, on C-1 and C-4), 4.33(H), 5.21 (4H) and 6.44 (NH, J=8 Hz). (Found: C, 50.31; H, 5.80; N, 3.81%). Lit. mp 147°C[1] and 138.5—140°C.[2]

(1,4/2,3,5)-5-Acetamido-1,2,3,4-tetra-O-trideuterioacetyl-1,2,3,4-cyclopentanetetrol (**4**). A 0.12 g protion of **5** was treated with 0.7 ml of acetic anhydride-d_6 in 2.5 ml of pyridine to give 0.18 g (78%) of the product, mp 144—145°C. PMR: δ 1.95 (3 protons, NAc), 4.34 (H), 5.24 (4H) and 6.28 (NH).

(1,4/2,3,5)-5-Acetamido-1,4-di-O-acetyl-2,3-di-O-trideuterioacetyl-1,2,3,4-cyclopentanetetrol (**16**). A 50 mg sample of **15** was treated with 0.5 ml of acetic anhydride-d_6 in pyridine (1.0 ml) to give 20 mg of the product, mp 145°C. PMR: δ 1.95 (3 protons, NAc), 2.08 (6 protons, OAc×2, on C-1 and C-4), 4.33 (H), 5.25 (4H) and 6.08 (NH).

(1,4/2,3,5)-5-Acetamido-1,2,3,4-cyclopentanetetrol (**5**). A 0.5 g portion of **3** was selectively de-*O*-acetylated in methanol (50 ml) saturated with ammonia. The solution was evaporated under reduced pressure and the residue was washed with ethyl acetate to give a crude product. Recrystallization from ethanol afforded 0.14 g (53%) of the product, mp 169.5—171°C.

Found: C, 44.02; H, 6.71; N, 7.12%. Calcd for $C_7H_{13}NO_5$: C, 43.97; H, 6.85; N, 7.33%.

(1,4/2,3,5)-5-Acetamido-1,4-di-O-acetyl-2,3-O-isopropylidene-1,2,3,4-cyclopentanetetrol (**6**). A mixture of **5** (87 mg), anhydrous acetone (50 ml) and methanol (5 ml) was agitated for 48 hr in the presence of Drielite and a half drop of conc sulfuric acid. The reaction mixture was neutralized to pH 7 with Amberlite IR-4B and then evaporated under reduced pressure to give a crystalline residue. The residue was acetylated to give a crude product. Recrystallization from ethanol afforded 89 mg (63%) of needles, mp 177—178°C. PMR: δ 1.29 (3 protons, CH_3), 1.51 (3 protons, CH_3), 1.91 (3 protons, NAc), 2.05 (6 protons, OAc×2), 4.55 (3H), 5.04 (2H) and 6.37 (NH, J=8 Hz).

Foudd: C, 53.61; H, 6.77; N, 4.36%. Calcd for $C_{14}H_{21}NO_7$: C, 53.32; H, 6.71; N, 4.44%.

(1,4/2,3,5)-5-Amino-1,2,3,4-cyclopentanetetrol (**7**). A 1.05 g portion of **3** was heated under reflux in 6 N hydrochloric acid for 2 hr. The solution was evaporated *in vacuo* to give 0.61 g of a residue, The residue was dissolved in water and treated with Amberlite IRA-400(OH^-). The aqueous solution was evaporated and the residue was crystallized in absolute ethanol (10 ml) to give 0.39 g (89%) of the product, mp 159—161°C. The product showed a positive ninhydrin test.

Found: C, 40.59; H, 7.25; N, 9.58%. Calcd for $C_5H_{11}NO_4$: C, 40.26; H, 7.43; N, 9.39%.

(1,4/2,3,5)-5-Acetamido-2,3-O-cyclohexylidene-1,2,3,4-cyclopentanetetrol (**8**). A 3.55 g portion of **2** was dissolved in methanol (100 ml) previously saturated with ammonia and the solution was settled overnight at room temperature. Evaporation of the solution under reduced pressure yielded an oily residue, which was triturated in a mixture of ethyl acetate (9 ml) and ether (15 ml) to give 1.89 g (70%) of the crude product. Recrystallization from ethyl acetate afforded 1.65 g (61%) of the crystals, mp 159.5—160.5°C.

Found: C, 57.31; H, 7.80; N, 5.14%. Calcd for $C_{13}H_{21}NO_5$: C, 57.55; H, 7.81; N, 5.16%.

(1,4/2,3,5)-5-Acetamido-2,3-O-cyclohexylidene-1,4-di-O-methanesulfonyl-1,2,3,4-cyclopentanetetrol (**9**). To 1.00 g of **8** in dry pyridine (20 ml) was added 0.8 ml of methanesulfonyl chloride with a mechanical agitation under ice cooling. The mixture was settled overnight at room temperature and then it was poured into 50 ml of ice and water. The aqueous solution was stored in a refrigerator to give 0.95 g (62%) of crystals, mp 112—116°C. PMR: δ 1.64 (10 protons, cyclohexylidene group), 2.03 (3 protons, NAc), 3.14 (6 protons, OMs×2), 4.84 (5H) and 6.61 (NH, J=8 Hz).

Found: C, 41.70; H, 6.09; N, 3.26; S, 13.83%. Calcd for $C_{15}H_{15}NS_2O_9$: C, 42.14; H, 5.89; N, 3.28; S, 15.00%.

An alternative method was as followings. The aqueous solution was extracted with chloroform (50 ml×4) and the chloroform extracts were evaporated under reduced pressure and the residue was added to 30 ml of water to give 1.07 g (69%) of crystals, mp 111—114°C. Recrystallization from an organic solvent resulted in a partial decomposition of the product.

(1,2,3,4,5)-5-Acetamido-1,2,3,4-tetra-O-acetyl-1,2,3,4-cyclopentanetetrol (**10**). A mixture of **9** (200 mg) and water (20 ml) was heated under reflux for 40 min and then evaporated under reduced pressure. The residue was acetylated as usual and the product was recrystallized from ethanol to give 83 mg (62%) of needles, mp 172—173°C. Admixture of **10** with (1,4,5/2,3)-isomer which was prepared by the method of Ahluwalia *et al.*[2] showed a remarkable depression of the melting point.

PMR (100 MHz): δ 2.04 (3 protons, NAc), 2.06 (6 protons, OAc×2), 2.13 (6 protons, OAc×2), 4.85 (H), 5.37 (4H) and 5.86 (NH, J=9 Hz).

Found: C, 49.87; H, 6.08; N, 3.97%. Calcd for $C_{15}H_{21}NO_9$: C, 50.13; H, 5.89; N, 3.90%.

DL-(1/2,3,4,5)-5-Acetamido-1,2,3,4-tetra-O-acetyl-1,2,3,4-cyclopentanetetrol (**12**). To a solution of **8** (0.5 g) in pyridine (10 ml) was added methanesulfonyl chloride (0.4 ml) with an agitation under ice cooling. After 65 min the mixture was poured into ice cold water (15 ml) and the aqueous solution was extracted with chloroform (40 ml×3). The combined chloroform extracts were washed with 0.1 N hydrochloric acid and water. Evaporation of chloroform yielded an oily product. Tlc on silica gel with benzene-ethanol (5 : 1) showed **9** at R_f 0.7 and monomethanesulfonyl derivative (**11**) at R_f 0.6 as two major components.

The mixture of **9** and **11** was heated in water (40 ml) under reflux for 3 hr and evaporated under reduced pressure. The residue was hydrolyzed in 80% aqueous acetic acid and the hydrolyzate was acetylated to give an oily product. The crude product was chromatographed on a silica gel column (Wako gel C-200, 25 g, 400×18 mm) with benzene-ethanol (5 : 1) as an eluant and each fraction (2 ml) was tested by tlc. A substance with R_f 0.66 was found in the fractions from 9th to 17th, which were combined and evaporated to give 0.33 g of a residue. The residue was crystallized in ether and recrystallized from ether to give 89 mg (14%) of the compound **12** as fine needles, mp 116°C. PMR:

δ 1.96 (3 protons, NAc), 2.01, 2.04, 2.06, 2.10 (3 protons each, OAc), 4.52 (H), 5.33 (4H) and 6.16 (NH, J=8 Hz).

Found: C, 50.21; H, 5.84; N, 3.92%. Calcd for $C_{15}H_{21}NO_9$: C, 50.13; H, 5.89; N, 3.90%.

The fractions from 18th to 35th contained a product of R_f 0.52, which were combined and evaporated. The residue was recrystallized from ethanol to give 115 mg (17%) of the compound **10**, mp 172—173°C, which was identified by a comparison of IR spectrum and a mixed melting point determination with an authentic sample.

*DL-(1,2,3/4,5)-5-Acetamido-1,4-di-O-acetyl-2,3-O-cyclohexylidene-1,2,3,4-cyclopentanetetrol (**13**).* The crystalline nitro compound **1** (1.86 g, mp 102—108°C) which was prepared by the method of Ahluwalia *et al.*[2] was hydrogenated in ethanol with Raney nickel T-4[8] and subsequently acetylated as described in the preparation of **2**. After 0.70 g of **2** was obtained from the benzene solution, the mother liquor was settled in a refrigerator for three days to give 0.19 g of the crude product, mp 185—188°C. The product was recrystallized from benzene to give 0.13 g (5%) of **13**, mp 186—188°C. PMR: δ 1.50, 1.68 (10 protons, cyclohexylidene group), 1.96 (3 protons, NAc), 2.10 (3 protons, OAc) and 2.12 (3 protons, OAc).

Found: C, 57.99; H, 7.25; N, 3.85%. Calcd for $C_{17}H_{25}NO_3$: C, 57.45; H, 7.09; N, 3.94%.

*DL-(1,2,3/4,5)-5-Acetamido-1,2,3,4-tetra-O-acetyl-1,2,3,4-cyclopentanetetrol (**14**).* A 72 mg portion of **13** was hydrolyzed in 6 N hydrochloric acid (10 ml) for 1 hr under reflux. The solution was evaporated *in vacuo* and the residue was acetylated to give a crude product. Recrystallization from ether afforded 52 mg (72%) of **14** as needle crystals, mp 187—188°C. PMR (100 MHz): δ 1.99 (3 protons, NAc), 2.06, 2.07, 2.11, 2.12 (3 protons each, OAc), 4.85 (H), 5.40 (4H) and 6.12 (NH, J=8 Hz).

Found: C, 50.54; G, 5.51; N, 3.96%. Calcd for $C_{15}H_{21}NO_9$: C, 50.13; H, 5.89; N, 3.90%.

An alternative method was as followings. The benzene mother liquor from which **2** had been obtained in the preparation of **2** beginning with an oily nitro compound **1** was evaporated to give a dark residue (3.8 g). The residue was hydrolyzed in 80% aqueous acetic acid and the hydrolyzate was acetylated. The acetylated product was dissolved in chloroform and the solution was decolorized with activated alumina and evaporated. The residue was crystallized in chloroform-ether to give 0.21 g of needles. Recrystallization from chloroform-ether afforded 172 mg of crystals, mp 187—188.5°C. The product was identified to be **14** by a comparison of IR spectrum and a mixed melting point determination with an above mentioned product. The product showed a single spot in tlc with benzene-ethanol (5 : 1).

*(1,4/2,3,5)-5-Acetamido-1,4-di-O-acetyl-1,2,3,4-cyclopentanetetrol (**15**).* Hydrolysis of **2** (1.88 g) in boiling 80% aqueous acetic acid (40 ml) for 40 min afforded an oily product, which showed two major eomponents on tlc with benzene-ethanol (5 : 1) at R_f 0.3 and 0.5. The crude product was crystallized in ethanol giving 0.77 g of crystals, mp 161—164°C. Recrystallization from ethanol afforded 0.62 g (42%) of **15**, mp 167—168.5°C.

Found; C, 48.30; H, 6.34; N, 5.41%. Calcd for $C_{11}H_{17}NO_7$: C, 48.00; H, 6.22; N, 5.09%.

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