Aminocyclitols. 30.[1] Unambiguous Synthesis of Seven Aminocyclopentanetetrols

TETSUO SUAMI,* KINNICHI TODANO, SHIGERU NISHIYAMA, AND F. W. LICHTENTHALER[2]

Department of Applied Chemistry, Faculty of Engineering, Keio University, Hiyoshi, Yokohama, Japan

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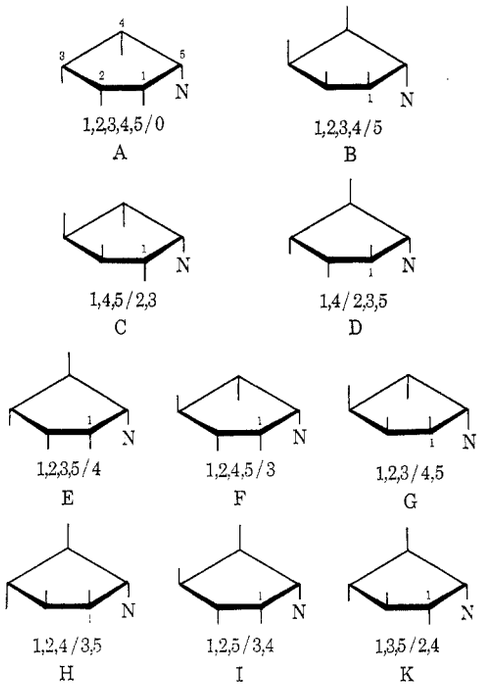
Pentaacetyl and other derivatives of 5-amino-1,2,3,4-cyclopentanetetrols with 1,2,3,5/4 (**14**), 1,2,3,4/5 (**15**), 1,4,5/2,3 (**16**), 1,3,5/2,4 (**17**), and 1,2,4/3,5 configuration (**18**) were prepared from readily accessible derivatives (**3** and **4**) of the 1,4/2,3,5 isomer. The synthetic routes involved displacement of sulfonyloxy group of the mono-*O*-sulfonyl (**1**, **5**, **11–13**) and di-*O*-sulfonyl derivatives (**8–10**) by water. In an analogous reaction sequence the pentaacetyl derivatives of 1,2,4,5/3 (**33**) and the all-cis configuration (**34**) were prepared from mesylates (**31** and **32**) of the 1,4,5/2,3 isomer.

Though none of the ten possible 5-amino-1,2,3,4-cyclopentanetetrols (*cf.* Chart I) has been encountered

CHART I

THE TEN DIASTEREOMERIC AMINOCYCLOPENTANETETROLS[a]



[a] Isomers A–D, having a plane of symmetry, are meso forms. Of the six racemic diastereomers E–K, the enantiomer has been depicted which allows clockwise assignment of positional numbers as in A.

in nature so far, their chemistry has received considerable attention,[3–5] deriving its main stimulus from the occurrence of certain aminocyclopentanepolyol systems as components in some antibiotics, *i.e.*, aristeromycin[6] and pactamycin.[7] While it might be surmised from the structural features of these antibiotics that aminocyclopentanepolyols as such may lack biological relevance, their preparation and establishment of configuration, nevertheless, was deemed prerequisite for further transformations, *i.e.*, conversions into nucleosides. As a consequence, in this paper we wish to report the preparation and configurational elucidation of seven diastereomers of pentaacetyl derivatives of 5-amino-1,2,3,4-cyclopentanetetrols, of which five had not been previously prepared, thus providing now a synthetic route to any one of the ten isomers.

DL-(1,2,3,5/4)-5-Amino-1,2,3,4-cyclopentanetetrol (E).—While the readily available 2,3-*O*-cyclohexylidene-(1,4/2,3,5)-5-acetamido-1,2,3,4-cyclopentanetetrol (**3**)[4,5] could be converted into the corresponding 1,4-di-*O*-mesyl derivative (**1**) in good yield (Chart II), selective mono-*O*-mesylation could not be achieved. Treatment of **3** with 1.1–1.4 molar equiv of mesyl chloride in each case yielded mixtures of the mono-*O*- and di-*O*-mesyl compounds (**2** and **1**) ranging in ratios from 1:1 to 3:2. After removal of the major portion of **1** formed, the resulting mixture of **1** and **2** was subjected to displacement of the sulfonyloxy group by heating in water in the presence of sodium acetate, and subsequently acetylated. On separation by column chromatography the crystalline 1,4-di-*O*-acetyl-2,3-*O*-cyclohexylidene-(1,2,3,5/4)-5-acetamido-1,2,3,4-cyclopentanetetrol (**7**) was obtained. Mild acid hydrolysis of **7** followed by acetylation afforded (1,2,3,5/4)-5-acetamido-1,2,3,4-cyclopentanetetrol tetraacetate (**14**), mp 123–124°.[8] The 1,2,3,5/4 configuration for **7** and **14** rests on the following evidence. First, compound **7** exhibited three and compound **14** five distinct acetyl resonances in the τ 8 region (*cf.* Table I), clearly indicating the presence of an unsymmetrical configuration (E–K, Chart I). Second, on displacement of the mesyloxy group of **2**, the 2,3 positions being sterically fixed by the cyclohexylidene group, configurational changes may occur at C-1 (or at C-4) and hence configuration E is left as the only choice for compounds **7** and **14**. This configurational assignment is further supported by the fact that the de-*O*-acetylated product of **14** (**19**) yields two distinct mono-*O*-isopropylidene derivatives (**20** and **21**) on acetonation. Formation of intermediary oxazolinium ions with participation of the vicinal trans acetamido groups and their cis opening by water were proposed as the reaction mechanism.[5]

(1,2,3,4/5)-5-Amino-1,2,3,4-cyclopentanetetrol (B).—On treatment of 1,4-di-*O*-acetyl-(1,4/2,3,5)-5-acetamido-1,2,3,4-cyclopentanetetrol (**4**)[5] with mesyl or tosyl chloride, in pyridine, the 2,3-di-*O*-mesyl (**8**) and 2,3-di-*O*-tosyl (**9**) derivatives were obtained. Each, on

(1) Part 29: T. Suami, S. Ogawa, H. Uchino, and M. Uchida, *Bull. Chem. Soc. Jap.*, in press.

(2) On leave of absence from Institut für Organische Chemie, Technische Hochschule Darmstadt, Germany.

(3) A. Hasegawa and H. Z. Sable, *J. Org. Chem.*, **31**, 4154 (1966).

(4) R. Ahluwalia, S. J. Angyal, and B. M. Luttrell, *Aust. J. Chem.*, **23**, 1819 (1970).

(5) T. Suami, Y. Sakota, K. Tadano, and S. Nishiyama, *Bull. Chem. Soc. Jap.*, **44**, 2222 (1971).

(6) T. Kusaka, H. Yamamoto, M. Shibata, M. Muroi, T. Kishi, and K. Mizuno, *J. Antibiot. (Tokyo), Ser. A*, **21**, 255 (1968).

(7) A. D. Argoudelis, H. K. Jahnke, and J. A. Fox, *Antimicrob. Ag. Chemother.*, 161 (1961); P. F. Wiley, H. K. Jahnke, F. McKellar, R. B. Kelly, and A. D. Argoudelis, *J. Org. Chem.*, **35**, 1420 (1970).

(8) The melting point previously reported for **14** (116°)[5] must be corrected, since further purification raised it to 123–124°.

CHART II

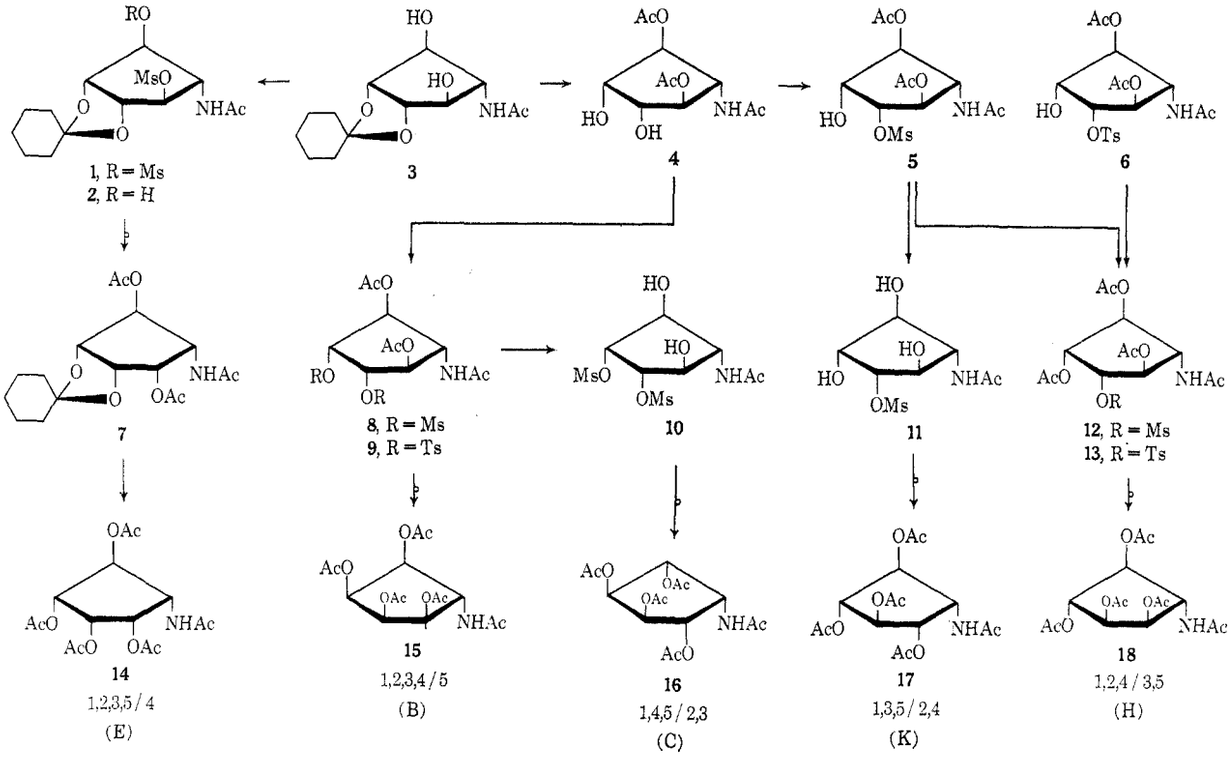
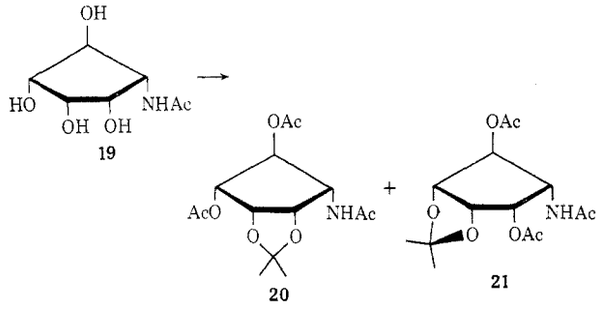


TABLE I

CHEMICAL SHIFT OF ACETYL RESONANCES IN $CDCl_3$ AND MELTING BEHAVIOR OF THE TEN 5-ACETAMIDO-1,2,3,4-CYCLOPENTANETETROL TETRAACETATES

Configuration		Acetyl resonances (τ value) (number of OAc groups)				
Formula	Fractional notation	OAc		NHAc[a]	Mp, °C	Ref
A (34)	1,2,3,4,5/0	7.91 (2)	7.92 (2)	8.03	174–175	5
B (15)	1,2,3,4/5	7.87 (2)	7.94 (2)	7.96	145–146	
C (16)	1,4,5/2,3	7.87 (2)	7.95 (2)	7.97	176.5	4
					173.5–174	5
D	1,4/2,3,5	7.92 (2)	7.95 (2)	8.05	147	3
					138.5–140	4
					148.5–149.5	5
E (14)	1,2,3,5/4	7.90, 7.94, 7.96, 7.99		8.04	123–124	
F (33)	1,2,4,5/3	7.85, 7.88, 7.93, 7.99		8.00	162–163.5	
G	1,2,3/4,5	7.88, 7.89, 7.93, 7.94		8.01	192	3
					189.5–190.5	5
H (18)	1,2,4/3,5	7.92, 7.94, 7.95, 7.96		8.04	111–112°	
I	1,2,4/3,4				119	3
K (17)	1,3,5/2,4	7.87, 7.90, 7.93 7.94		8.04	161.5–162.5	

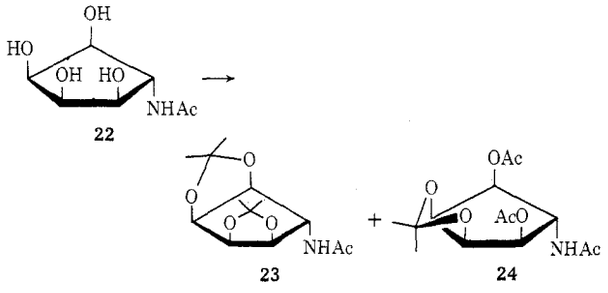
[a] Assignment of the *N*-acetyl resonance of the D isomer was established by measurement of the *O*-trideuterioacetyl derivative,[5] and those of the other isomers were carried out by analogy with that of the D isomer.



displacement of the sulfonyloxy group with water–sodium acetate, evidently proceeding *via* cyclic acetoxonium ions by participation of the vicinal trans acetoxy groups and their respective cis opening by water,[9] and subsequent acetylation afforded the pentaacetyl derivative (**15**), mp 145–146°. The 1,2,3,4/5 configuration for this compound was established on the basis of the following findings. The nmr spectrum of **15** revealed three sharp signals with 2:2:1 relative intensities for the five acetyl groups, clearly indicating the presence of a symmetrical structure (A–D). Three of the four compounds had been described[3–5] (A, C, and D) and compound **15** was not identical with any one of the known pentaacetyl derivatives by comparing their melting point, nmr, and ir spectra. Therefore, configuration B is given to compound **15**. The assign-

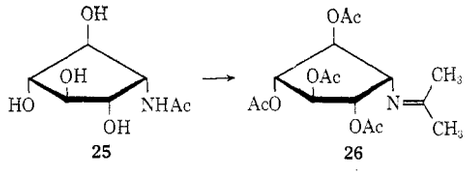
(9) H. Paulsen, *Advan. Carbohyd. Chem.*, **26**, 133 (1971).

ment of the configuration is consistent with the fact that the de-*O*-acetylated product of **15** (**22**) yielded mono-*O*-isopropylidene (**24**) and di-*O*-isopropylidene derivative (**23**) on acetonation.

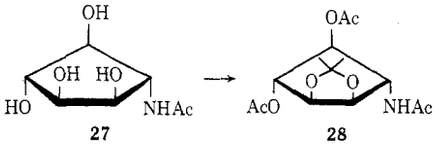


(1,4,5/2,3)-5-Amino-1,2,3,4-cyclopentanetetrol (C).—In contrast to reactions of **8** and **9** → **15**, the analogous reaction with the de-*O*-acetylated product of **8** (**10**) took —not unexpectedly—a different course. By participation of the neighboring hydroxyl groups, the reaction proceeded *via* oxirane intermediates. The oxirane rings were opened in the trans arrangement by intramolecular attack of the vicinal acetamido groups, forming oxazolinium ions, which were further attacked by water to give *cis*-acetamido alcohol. Thus the pentaacetyl derivative of the 1,4,5/2,3 configuration (**16**) was obtained on acetylation as the main product, identical with a sample prepared by another route.[4]

DL-(1,3,5/2,4)-5-Amino-1,2,3,4-cyclopentanetetrol (K).—Mesylation of **4** gave a mixture of the mono-*O*-mesyl (**5**) and di-*O*-mesyl (**8**) compounds, which were successfully separated. De-O-acetylation of **5** yielded the mono-*O*-mesyl derivative (**11**), which on treatment in water–sodium acetate and subsequent acetylation afforded the (1,3,5/2,4)-5-acetamido-1,2,3,4-cyclopentanetetrol tetraacetate (**17**), mp 161.5–162.5°. The nmr spectrum of **17** exhibited five sharp acetyl resonances in the τ 8 region, thus establishing an unsymmetric configuration (E–K). Comparisons of ir data and melting behavior with that of four other pentaacetyl derivatives (configuration E–H) showed **17** to be not identical with any of the four compounds, and formation of a compound with configuration I could not be conceived in the reaction employed. Therefore, **17** was reasonably assigned the 1,3,5/2,4 configuration. This assignment was supported by the fact that an *N*-isopropylidene derivative (**26**) was formed but no *O*-isopropylidene derivative was formed on treatment of the de-O-acetylated product of **17** (**25**) with 2,2-dimethoxypropane in the presence of *p*-toluenesulfonic acid and subsequent acetylation. The analogous reaction mechanism *via* oxirane intermediates as described above was proposed in this reaction.



DL-(1,2,4/3,5)-5-Amino-1,2,3,4-cyclopentanetetrol (H).—By comparison with the stereochemical course of other reactions in acetamidocyclopentanetetrol series, *i.e.*, conversions of **8** and **9** → **15**, **31** → **33**, **32** → **34**, and other examples,[5] displacement of the mesyloxy group in **5** would be expected to yield a product of 1,2,4/3,5 configuration (H). The same would have to be anticipated for the tosyl analog (**6**) and their fully acetylated products (**12** and **13**). Indeed, when subjecting either of them to the displacement reaction by water–sodium acetate, followed by acetylation, the pentaacetyl derivative (**18**), mp 111–112°, was obtained as the exclusive product. The ease with which the reactions of **5**, **6**, **12**, and **13** took place to give **18**, together with the fact that no other isomeric products were detectable by tlc in the reaction mixture, already appears to be convincing proof of the validity of the mechanistic rationalizations advanced above, and hence of the 1,2,4/3,5 configuration of **18**. Corroborative evidence is provided by the nmr pattern of acetyl resonances, exhibiting five sharp signals in the τ 8 region (Table I) to indicate an unsymmetrical configuration (E–K), and by the nonidentity of **18** with any one of the eight other pentaacetyl derivatives in our hands (A–G and K) with respect to ir, melting point, and mixture melting point data.[10] Thus, **18** can unequivocally be assigned the 1,2,4/3,5 configuration. A formation of a mono-*O*-isopropylidene derivative (**28**) from the de-O-acetylated



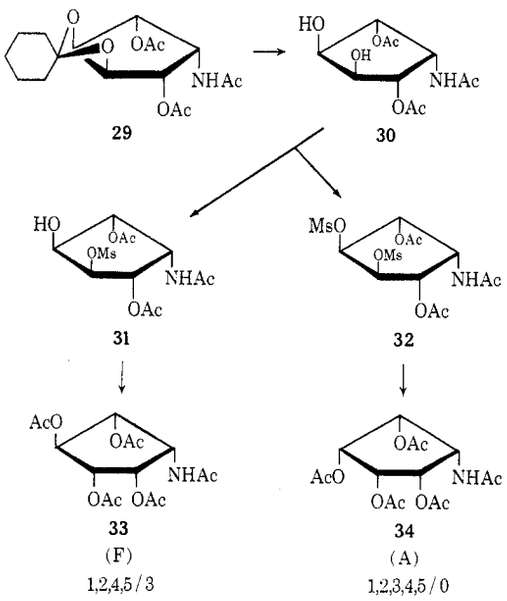
product of **18** (**27**) provided further evidence for the assigned configuration. In fact, a pentaacetyl derivative of the 1,2,4/3,5 configuration with mp 123–124° was reported by Hasegawa and Sable[3] (compound XXVIb). Although the melting point of our product **18** (111–112°) is rather close, the two compounds were found to be not identical with respect to ir and mixture melting point.[11] In addition, an analogous comparison of XXVIb[3] with the above-described **14** showed no depression of the mixture melting point (123–124°) and exhibited only minor differences in their ir spectra.[11] Since the configurational proof for **14** and **18** is unequivocal, it appears likely that the configuration of compound XXVIb[3] will have to be revised to 1,2,3,5/4 arrangement of substituents.

DL-(1,2,4,5/3)- (F) and (1,2,3,4,5/0)-5-Amino-1,2,3,4-cyclopentanetetrol (A).—Application of the reaction sequences similar to those used for the conversions **4** → **5** → **18** and **4** → **8** → **15** to compound **30** available from **29**[4] could give the known isomer **34**[5] and its C-3 epimer **33**. Mesylation of **30** yielded the expected mixture of mono-*O*- and di-*O*-mesyl derivatives (**31** and **32**, respectively), which was subjected to displacement of

(10) The pentaacetyl derivative obtained (**18**) might be surmised to have the 1,2,5/3,4 configuration (I), the only isomer not at hand for direct comparison. Its reported melting point (119°[3] *vs.* 111–112° of **18**; *cf.* Table I) is very similar; it would feature an analogous pattern of acetyl resonances and also could give a mono-*O*-isopropylidene compound, although a di-*O*-isopropylidene derivative would be more likely. However, a product with a configuration as in I cannot intelligibly be conceived to arise from compounds of a 1,4/2,3,5 arrangement of substituents as in **5**, **6**, **12**, and **13**.

(11) Dr. H. Z. Sable, School of Medicine, Case Western Reserve University, Cleveland, Ohio 44106, kindly performed these comparative measurements.

the mesyloxy group with water–sodium acetate and subsequent acetylation to give a mixture of **33** and **34**.



Separation was achieved by column chromatography and afforded the major product, the F isomer **33**, mp 162–163.5°, while the A isomer **34** was isolated as the minor product, which was identified with an authentic sample.[5] The 1,2,4,5/3 configuration for **33** clearly followed from its nmr pattern of acetyl resonance signals (Table I), from its nonidentity with eight of the other nine isomers (A–E, G, H, and K)—the mixture melting point of **33** with **16**, **17**, and **34** showed strong depression—and from the fact that a compound of configuration F is the only reasonable product to be expected in this reaction.

Experimental Section

General.—Melting points were determined in capillary tubes and are corrected. Solutions were evaporated under diminished pressure. Acetylations were carried out with acetic anhydride in pyridine in the usual manner. Ir spectra were determined for potassium bromide disks with a Hitachi EPI-2 spectrophotometer. Nmr spectra were measured at 60 and 100 MHz on a Varian A-60D and a Varian HA-100D spectrometer in deuteriochloroform with reference to tetramethylsilane as an internal standard and the peak positions are given in τ values. Tlc was performed on silica gel plates (Wakogel B-10) with 5:1 benzene–ethanol as a solvent system, if not indicated otherwise. Elemental analyses were performed by Mr. Saburo Nakada, to whom our thanks are due.

A. Derivatives of (1,4/2,3,5)-5-Amino-1,2,3,4-cyclopentanetetrol (5, 6, and 8–13). 1,4-Di-*O*-acetyl-2- (or 3-) *O*-mesyl-(1,4/2,3,5)-5-acetamido-1,2,3,4-cyclopentanetetrol (5).—To a solution of 1,4-di-*O*-acetyl-(1,4/2,3,5)-5-acetamido-1,2,3,4-cyclopentanetetrol (**4**)[6] (1.00 g, 3.6 mmol) in pyridine was added mesyl chloride (0.40 ml, 5.2 mmol). The solution was left overnight at room temperature and poured into ice water to give di-*O*-mesyl derivative **8** (0.44 g) as a crystalline precipitate, which was collected by filtration. The filtrate was extracted with chloroform and the chloroform solution was evaporated. The residue was crystallized from ethanol, giving **5** (0.50 g, 39%), mp 141–145°. Recrystallization from ethyl acetate yielded the analytical sample, mp 151–152°.

Anal. Calcd for $C_{12}H_{19}NO_9S$: C, 40.77; H, 5.44; N, 3.96; S, 9.06. Found: C, 40.60; H, 5.19; N, 4.04; S, 8.96.

1,4-Di-*O*-acetyl-2,3-di-*O*-mesyl-(1,4/2,3,5)-5-acetamido-1,2,3,-4-cyclopentanetetrol (8).—To a solution of **4** (0.61 g, 2.2 mmol) in pyridine (8.0 ml), mesyl chloride (0.65 ml, 8.3 mmol) was added with cooling and stirring. The mixture was then kept at room temperature overnight and stirred into ice water to give crystalline precipitate. Collection by filtration, washing with cold water, and drying afforded **8** (0.62 g, 65%) as colorless crystals, mp 173–176°. Extraction of the aqueous filtrate with ethyl acetate gave another crop (0.20 g, 21%): nmr (5:1 $CDCl_3$–pyridine-d_5) τ 8.03 (s, 3 H, NHAc), 8.01 (s, 6 H, 2 OAc), 6.73 (s, 6 H, 2 OMs).

Anal. Calcd for $C_{13}H_{21}NO_{11}S_2$: C, 36.18; H, 4.92; N, 3.25; S, 14.84. Found: C, 36.13; H, 4.96; N, 3.40; S, 14.79.

Tosylation of 1,4-Di-*O*-acetyl-(1,4/2,3,5)-5-acetamido-1,2,3,4-cyclopentanetetrol (4).—To a solution of **4** (0.50 g, 1.8 mmol) in pyridine (12 ml), a mixture of tosyl chloride (1.73 g, 9.1 mmol) and pyridine (3.5 ml) was added under ice cooling with agitation. After stirring for 4 hr, the solution was poured into ice water, which subsequently was extracted with chloroform. Evaporation of the extract gave a mixture of **6** and **9**, which was fractionated on a silica gel column (Wakogel C-200, 30 g) with 8:1 benzene–ethanol.

Di-*O*-tosylate 9.—The fractions containing **9** according to tlc (R_f 0.6 in the same solvent system as above) were pooled and evaporated. The residue crystallized on trituration with ethyl acetate–petroleum ether (bp 30–60°) to give needles (0.32 g 30%), mp 144–145°. Recrystallization from chloroform–petroleum ether gave the analytically pure sample: mp 150–151°; nmr τ 8.09 (s, 3 H, NHAc), 8.05 (s, 6 H, 2 OAc), 7.53 (s, 6 H, aryl CH_3).

Anal. Calcd for $C_{25}H_{29}NO_{11}S_2$: C, 51.44; H, 5.01; N, 2.40; S, 10.97. Found: C, 51.70; H, 4.89; N, 2.43; S, 11.39.

Mono-*O*-tosylate 6.—The appropriate fractions containing **6** (R_f 0.5 in the same solvent system as above) were combined and evaporated to dryness. The residue was crystallized from ethyl acetate–petroleum ether to afford **6** (0.30 g, 38%): mp 153–154°; nmr τ 8.09 (s, 3 H, NHAc), 7.90 (s, 6 H, 2 OAc), 7.54 (s, 3 H, aryl CH_3).

Anal. Calcd for $C_{18}H_{23}NO_9S$: C, 50.33; H, 5.41; N, 3.26; S, 7.46. Found: C, 50.47; H, 5.28; N, 3.25; S, 7.08.

2,3-Di-*O*-mesyl-(1,4/2,3,5)-5-acetamido-1,2,3,4-cyclopentanetetrol (10).—Compound **8** (1.44 g) was dissolved in methanolic ammonia (40 ml) and the solution was stored in a refrigerator overnight. Evaporation and recrystallization of the residue from ethanol afforded **10** (0.92 g, 79%), mp 137–138°.

Anal. Calcd for $C_9H_{17}NO_9S_2$: C, 31.11; H, 4.93; N, 4.03; S, 18.44. Found: C, 30.87; H, 4.97; N, 4.02; S, 18.22.

2- (or 3-) *O*-Mesyl-(1,4/2,3,5)-5-acetamido-1,2,3,4-cyclopentanetetrol (11).—De-O-acetylation of **5** (0.49 g) in methanolic ammonia (12 ml) and work-up as described for **10** gave 0.28 g (76%) of crude product, which after recrystallization from ethanol melted at 177–178°.

Anal. Calcd for $C_8H_{15}NO_7S$: C, 35.67; H, 5.61; N, 5.20; S, 11.89. Found: C, 36.00; H, 5.52; N, 5.20; S, 11.36.

1,3,4-Tri-*O*-acetyl-2-*O*-mesyl-(1,4/2,3,5)-5-acetamido-1,2,3,4-cyclopentanetetrol (12).—Acetylation of **5** (97 mg) in the usual manner and recrystallization of the crude product (mp 149–151°) from ethanol afforded **12** (58 mg, 54%) as colorless crystals: mp 151–152°; nmr τ 8.02 (s, 3 H, NHAc), 7.89 (s, 3 H, OAc), 7.88 (s, 6 H, 2 OAc), 6.90 (s, 3 H, OMs), 3.65 (d, 1 H, J = 7 Hz, NH).

Anal. Calcd for $C_{14}H_{21}NO_{10}S$: C, 42.54; H, 5.36; N, 3.54; S, 8.11. Found: C, 42.33; H, 5.10; N, 3.58; S, 8.30.

1,3,4-Tri-*O*-acetyl-2-*O*-tosyl-(1,4/2,3,5)-5-acetamido-1,2,3,4-cyclopentanetetrol (13).—Acetylation of tosylate **6** (200 mg) and recrystallization of the crude product from acetone–ethyl acetate afforded **13** (0.15 g, 68%): mp 188–191°; nmr τ 8.07 (s, 3 H, NHAc), 8.04, 7.98, and 7.92 (three s, 3 H, 3 OAc), 7.54 (s, 3 H, aryl CH_3).

Anal. Calcd for $C_{20}H_{25}NO_{10}S$: C, 50.93; H, 5.35; N, 2.97; S, 6.79. Found: C, 50.93; H, 5.13; N, 3.21; S, 6.90.

B. Derivatives of DL-(1,2,3,5/4)-5-Amino-1,2,3,4-cyclopentanetetrol (7, 14, and 19–21). 1,4-Di-*O*-acetyl-2,3-*O*-cyclohexylidene-DL-(1,2,3,5/4)-5-acetamido-1,2,3,4-cyclopentanetetrol (7).—2,3-*O*-Cyclohexylidene-(1,4/2,3,5)-5-acetamido-1,2,3,4-cyclopentanetetrol (**3**)[5] (950 mg, 3.5 mmol) was treated with mesyl chloride (0.41 ml, 5.3 mmol) in pyridine (12 ml) for 30 min under ice cooling and agitation. The mixture was left at room temperature for 1.5 hr and poured into ice water (100 ml) to give the 1,4-di-*O*-mesylate (**1**)[5] as a crystalline precipitate, which was collected by filtration (394 mg). Extraction of the filtrate with chloroform, followed by washing of the organic layer with water, drying, and evaporation, gave an oily residue (831 mg) comprising according to tlc an approximately 3:2 mixture of monomesylate **2** and dimesylate **1**. This mixture was treated with boiling water

in the presence of sodium acetate (0.98 g) for 1.5 hr and subsequently evaporated to dryness. Upon acetylation of the residue, the mixture was separated on a silica gel column (Wakogel C-200, 75 g, 35 × 1.8 cm) by elution with 10:1 benzene–ethanol. The fractions containing **7** according to tlc were pooled and evaporated to dryness. Trituration with ether afforded 288 mg (23%) of **7** as colorless crystals: mp 98–100°; nmr τ 8.45 and 8.30 (two m, 4 H and 6 H, cyclohexylidene protons), 8.02 (s, 3 H, NHAc), 7.92 and 7.86 (two s, 3 H, 2 OAc).

Anal. Calcd for $C_{17}H_{25}NO_7$: C, 57.45; H, 7.09; N, 3.94. Found: C, 57.29; H, 6.94; N, 3.89.

Tetra-*O*-acetyl-DL-(1,2,3,5/4)-5-acetamido-1,2,3,4-cyclopentanetetrol (14).—The cyclohexylidene compound **7** (100 mg) was refluxed in 80% aqueous acetic acid for 70 min and the solution was subsequently evaporated to dryness. Acetylation of the residue as usual and recrystallization of the crude product from ether afforded **14** (54 mg, 54%) as needles, mp 123–124°.[8] Nmr data (*cf.* Table I) were identical with those of the compound described previously.[5]

Anal. Calcd for $C_{15}H_{21}NO_9$: C, 50.13; H, 5.89; N, 3.90. Found: C, 50.11; H, 6.02; N, 3.90.

DL-(1,2,3,5/4)-5-Acetamido-1,2,3,4-cyclopentanetetrol (19).—De-O-acetylation of **14** (400 mg) with methanolic ammonia overnight and evaporation of the reaction mixture followed by two recrystallizations from ethanol afforded 145 mg (68%) of colorless crystals, mp 123–124°.

Anal. Calcd for $C_7H_{13}NO_5$: C, 44.22; H, 6.75; N, 7.18. Found: C, 43.98; H, 6.85; N, 7.33.

3,4-Di-*O*-acetyl-1,2-*O*-isopropylidene- (20) and 1,4-di-*O*-acetyl-2,3-*O*-isopropylidene-DL-(1,2,3,5/4)-5-acetamido-1,2,3,4-cyclopentanetetrol (21).—To a solution of acetamidotetrol **19** (85 mg) in 12 ml of 1:1 acetone–methanol, Drierite (0.3 g) and a drop of concentrated sulfuric acid were added. The mixture was stirred for 46 hr and then neutralized with sodium bicarbonate solution, followed by extraction with chloroform and evaporation of the extract. The residue was acetylated to give a syrup (172 mg) comprising according to tlc an approximately 4:1 mixture of two products (R_f 0.67 and 0.54, respectively). Separation was achieved on a silica gel column (Wakogel C-200, 35 g, 30 × 2 cm) by elution with 5:1 benzene–ethanol. The appropriate fractions were pooled and evaporated to dryness. The major product (113 mg) was recrystallized from ether and again from ether–light petroleum to give 40 mg (29%) of an isopropylidene di-*O*-acetate (tentative structure **21**): mp 136–138°; nmr τ 8.69 and 8.48 [two s, 3 H, $C(CH_3)_2$], 8.02 (s, 3 H, NHAc), 7.94 and 7.90 (two s, 3 H, 2 OAc).

Anal. Calcd for $C_{14}H_{21}NO_7$: C, 53.32; H, 6.71; N, 4.44. Found: C, 53.44; H, 6.58; N, 4.36.

The minor product (25 mg, mp 154–156°) was recrystallized from ether to give 10 mg (7%) of di-*O*-acetylisopropylidene derivative **20** (tentatively): mp 155–156°; nmr τ 8.68 and 8.48 [two s, 3 H, $C(CH_3)_2$], 8.02 (s, 3 H, NHAc), 7.93 and 7.85 (two s, 3 H, 2 OAc).

Anal. Calcd for $C_{14}H_{21}NO_7$: C, 53.32; H, 6.71; N, 4.44. Found: C, 53.52; H, 6.76; N, 4.30.

C. Derivatives of (1,2,3,4/5)-5-Amino-1,2,3,4-cyclopentanetetrol (14 and 22–24). Tetra-*O*-acetyl-(1,2,3,4/5)-5-acetamido-1,2,3,4-cyclopentanetetrol (15). 1. From Dimesylate 8.—A suspension of **8** (0.61 g) in 30 ml of water containing 0.23 g of sodium acetate was refluxed for 10 hr. The solution was then evaporated and the residue was acetylated as usual. Crystallization of the product from ethyl acetate gave 0.28 g (55%), mp 141–145°. Recrystallization from chloroform–ether raised the melting point to 145–146° (0.11 g, 22%). A mixture melting point with tetra-*O*-acetyl-(1,4/2,3,5)-5-acetamido-1,2,3,4-cyclopentanetetrol[4] showed a remarkable depression.

Anal. Calcd for $C_{15}H_{21}NO_9$: C, 50.11; H, 5.90; N, 3.90. Found: C, 50.38; H, 5.95; N, 3.98.

2. From Ditosylate 9.—Refluxing **9** (400 mg) in 30 ml of 30% aqueous ethanol containing 0.12 g of sodium acetate for 24 hr, followed by acetylation and work-up as described under 1, gave 61 mg (25%) of **15**, identical in all respects with the product obtained above.

(1,2,3,4/5)-5-Acetamido-1,2,3,4-cyclopentanetetrol (22).—Compound **15** (0.19 g) was dissolved in methanolic ammonia (10 ml) and kept overnight. The solution was evaporated and the residue was triturated in ethyl acetate to give a crude product. Recrystallization from ethanol afforded **22** (77 mg, 76%), mp 173–176°. Admixture with the 1,4/2,3,5 isomer (mp 169.5–171°[5]) showed considerable depression of the melting point.

Anal. Calcd for $C_7H_{13}NO_5$: C, 43.96; H, 6.86; N, 7.33. Found: C, 43.64; H, 6.80; N, 7.21.

1,2:3,4-Di-*O*-isopropylidene- (23) and 1,4-Di-*O*-acetyl-2,3-*O*-isopropylidene-(1,2,3,4/5)-5-acetamido-1,2,3,4-cyclopentanetetrol (24).—To a solution of **22** (100 mg) in 66 ml of acetone–methanol (10:1), Drierite (0.30 g) and a drop of concentrated sulfuric acid were added. The mixture was stirred for 46 hr and then neutralized with sodium hydrogen carbonate solution, followed by extraction with chloroform and evaporation of the extract. The residue resisted crystallization despite several purifications *via* alumina columns. The product **23** of the tentative structure was characterized as a syrup (84 mg, 59%), exhibiting the presence of two isopropylidene functions (two s, 6 H at 8.68 and 8.42) and an acetamido group (s, 3 H at 8.03) in the nmr spectrum. The aqueous layer was evaporated to dryness, followed by acetylation of the residue and usual work-up. Crystallization was achieved from chloroform–ether to give the mono-*O*-isopropylidene derivative of the tentative structure **24** as needles (33 mg, 22%): mp 204–205°; nmr τ 8.67 and 8.45 [two s, 3 H, $C(CH_3)_2$], 8.04 (s, 3 H, NHAc), 7.87 (s, 6 H, 2 OAc).

Anal. Calcd for $C_{14}H_{21}NO_7$: C, 53.32; H, 6.71; N, 4.44. Found: C, 53.06; H, 6.58; N, 4.73.

D. Derivatives of (1,4,5/2,3)-5-Amino-1,2,3,4-cyclopentanetetrol (16 and 30–32). Tetra-*O*-acetyl-(1,4,5/2,3)-5-acetamido-1,2,3,4-cyclopentanetetrol (16).—A solution of dimesylate **10** (500 mg) and sodium acetate (0.22 g) in water (20 ml) was heated under reflux for 56 hr. Evaporation of the solution and acetylation of the residue gave a syrup which crystallized from ethyl acetate–petroleum ether: 150 mg (26%) of **16** as colorless crystals; mp 171–173°; for nmr *cf.* Table I. The product was identical on the basis of mixture melting point and ir data with the corresponding pentaacetyl derivative prepared by the method of Ahluwalia, *et al.*[4]

1,4-Di-*O*-acetyl-(1,4,5/2,3)-5-acetamido-1,2,3,4-cyclopentanetetrol (30).—A 0.55-g portion of 1,4-di-*O*-acetyl-2,3-*O*-cyclohexylidene-(1,4,5/2,3)-5-acetamido-1,2,3,4-cyclopentanetetrol[4] (**29**) was hydrolyzed in boiling 80% aqueous acetic acid (20 ml) for 100 min and then evaporated. The residue showed a major component (R_f 0.6) and a minor one (R_f 0.3) on tlc, and was fractionated on a silica gel column (Wakogel C-200, 30 g) with 5:1 benzene–ethanol. The main component was collected and evaporated to give 0.21 g (53%) of a colorless sirup.

Mixture of 1,4-Di-*O*-acetyl-2,3-di-*O*-mesyl- (32) and 1,4-Di-*O*-acetyl-2- (or 3-) *O*-mesyl-(1,4,5/2,3)-5-acetamido-1,2,3,4-cyclopentanetetrol (31).—To a solution of **30** (0.21 g, 0.8 mmol) in pyridine (3.0 ml) was added mesyl chloride (0.14 ml, 1.8 mmol) under ice cooling and the mixture was kept overnight at room temperature. The solution was poured into ice water and deionized with Amberlite MB-3. The solution was evaporated and the residue was chromatographed on a silica gel column (Wakogel C-200, 30 g) in 5:2 benzene–methanol. The two major components were collected and evaporated to give a mixture of **31** and **32** (0.27 g) as an amorphous solid.

E. Derivatives of DL-(1,3,5/2,4)-5-Amino-1,2,3,4-cyclopentanetetrol (17, 25 and 26). Tetra-*O*-acetyl-DL-(1,3,5/2,4)-5-acetamido-1,2,3,4-cyclopentanetetrol (17).—Refluxing **11** (0.25 g) with sodium acetate (0.12 g) in water (15 ml) for 17 hr, followed by evaporation and acetylation, afforded a product which crystallized from ethyl acetate (0.17 g, 51%, mp 159–161°). Recrystallization from ethyl acetate–petroleum ether gave analytically pure **17**, mp 161.5–162.5°; for nmr *cf.* Table I.

Anal. Calcd for $C_{15}H_{21}NO_9$: C, 50.11; H, 5.90; N, 3.90. Found: C, 49.77; H, 5.71; N, 3.88.

DL-(1,3,5/2,4)-5-Acetamido-1,2,3,4-cyclopentanetetrol (25).—Compound **17** (138 mg) was de-O-acetylated as described for **22**, and the crude product was recrystallized from ethanol to give **25** (49 mg, 52%), mp 166–167°, showing a single spot on tlc in chloroform–methanol (7:3).

Anal. Calcd for $C_7H_{13}NO_5$: C, 43.98; H, 6.85; N, 7.33. Found: C, 44.31; H, 7.01; N, 7.38.

Tetra-*O*-acetyl-*N*-isopropylidene-DL-(1,3,5/2,4)-5-amino-1,2,3,4-cyclopentanetetrol (26).—To a solution of **25** (30 mg) in *N*,*N*-dimethylformamide (2 ml), 2,2-dimethoxypropane (0.1 ml) and *p*-toluenesulfonic acid (3 mg) were added and the mixture was kept for 3 hr at room temperature. Neutralization by addition of Amberlite IRA-400 (OH^-) followed by evaporation and acetylation as usual gave a syrup which crystallized on trituration with ether: 35 mg (63%) of colorless crystals; mp 194–196°; nmr τ 8.47 and 8.28 [two s, 3 H, $C(CH_3)_2$], 7.97 and 7.94 (two s, 6 H, 4 OAc).

Anal. Calcd for $C_{16}H_{23}NO_8$: C, 53.77; H, 6.48; N, 3.92. Found: C, 53.50; H, 6.22; N, 4.07.

F. Derivatives of DL-(1,2,4/3,5)-5-Amino-1,2,3,4-cyclopentanetetrol (18, 27, and 28). Tetra-*O*-acetyl-DL-(1,2,4/3,5)-5-acetamido-1,2,3,4-cyclopentanetetrol (18). 1. From 6 or 5.—A mixture of 0.23 g (0.55 mmol) of 6 (or the molar equivalent of mesylate 5) and sodium acetate (0.1 g) was refluxed in water (10 ml) for 2 hr and evaporated. The residue was acetylated and the product was crystallized in ether to give 0.12 g (63%) of 18, mp 108–110°. Recrystallization from the same solvent raised the melting point to 111–112°. Mixture melting points with the pentaacetyl derivatives of configuration 1,2,3,5/4 (14, mp 123–124°), as well as 1,2,3,4/5 (15, mp 145–146°) and 1,4/2,3,5 (mp 148.5–149°) showed marked depression in each case; for nmr *cf.* Table I.

Anal. Calcd for $C_{15}H_{21}NO_9$: C, 50.11; H, 5.90; N, 3.90. Found: C, 50.53; H, 6.02; N, 3.84.

2. From 12 or 13.—A mixture of 0.85 g (1.41 mmol) of 13 (or the molar equivalent of 12), sodium acetate (0.3 g), and water (40 ml) was refluxed for 17 hr. Evaporation, acetylation, and work-up in the same manner as described under 1 afforded 0.44 g (67%) of 18, identical in all respects with the product described above.

DL-(1,2,4/3,5)-5-Acetamido-1,2,3,4-cyclopentanetetrol (27).—Compound 18 was de-O-acetylated with methanolic ammonia as described for 22 and the syrupy product obtained after evaporation was extracted with hot ethyl acetate. Only part of the residue which was insoluble in ethyl acetate, showing a single spot on tlc, could be induced to crystallization on trituration with 4:1 2-propanol–ethanol; 36 mg (43%) of colorless crystals, mp 142–144°, was obtained.

Anal. Calcd for $C_7H_{13}NO_5$: C, 43.83; H, 6.86; N, 7.28. Found: C, 44.31; H, 7.01; N, 7.38.

3,4-Di-*O*-acetyl-1,2-*O*-isopropylidene-DL-(1,2,4/3,5)-5-acetamido-1,2,3,4-cyclopentanetetrol (28).—Compound 27 (70 mg) was treated in *N,N*-dimethylformamide (3.5 ml) with 2,2-dimethoxypropane (0.20 ml) and *p*-toluenesulfonic acid (3 mg) for 3 hr at room temperature. Neutralization, acetylation, and work-up as described above for 26 gave a syrup which crystallized from ether: 50 mg (44%) of colorless crystals; mp 135–136°; nmr τ 8.71 and 8.43 [two s, 3 H, $C(CH_3)_2$], 8.01 (s, 3 H, HNAc), 7.94 and 7.92 (two s, 3 H, 2 OAc).

Anal. Calcd for $C_{14}H_{21}NO_7$: C, 53.32; H, 6.71; N, 4.44. Found: C, 53.37; H, 6.63; N, 4.45.

G. Tetra-*O*-acetyl-(1,2,3,4,5/0)-5-acetamido-1,2,3,4-cyclopentanetetrol (34).—A mixture (0.25 g) of the mono- and di-*O*-mesyl derivatives (31 and 32), as obtained on mesylation of 30 (*cf.* section C), was heated in water (10 ml) in the presence of sodium acetate (0.12 g) for 8 hr and subsequently evaporated. The residue was acetylated to give a syrupy mixture of 33 and 34, which was chromatographed on a silica gel column (Wakogel C-200, 30 g) in 5:1 benzene–ethanol. Fractions showing R_f 0.39 (tlc) were combined and evaporated to dryness. The residue was crystallized in ethanol to give 34 (17 mg, 6% from 30), mp 173–174°. The product was identified by a comparison of ir spectra and a mixture melting point determination with an authentic sample of 34, prepared by another route.[5]

H. Tetra-*O*-acetyl-DL-(1,2,4,5/3)-5-acetamido-1,2,3,4-cyclopentanetetrol (33).—Those fractions of the above column separation exhibiting a spot at R_f 0.41 (tlc) were pooled and evaporated to dryness. The residue was crystallized in ethyl acetate–petroleum ether to give 33 (60 mg, 22% from 30), mp 160–161°. Recrystallization from the same solvent yielded the analytically pure sample, mp 162–163.5°. Admixture with the 1,3,5/2,4 analog 17 (mp 161.5–162.5°) showed a distinct depression of the melting point.

Anal. Calcd for $C_{15}H_{21}NO_9$: C, 50.11; H, 5.90; N, 3.90. Found: C, 50.35; H, 5.80; N, 3.97.

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Synthesis of Some 17-Substituted 3,10-Ethano-5α-estranes[1]

FRANK M. HAUSER, ABRAHAM PHILIP, AND F. I. CARROLL*

Chemistry and Life Sciences Division, Research Triangle Institute, Research Triangle Park, North Carolina 27709

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Several 17-substituted derivatives of 3-hydroxy-3,10-ethano-5α-estrane were prepared. The synthetic sequence centers about the transformation of dehydroisoandrosterone 3-acetate (4a) into a 19a-methylandrostane-3,17,19-trione (7e). Treatment of 7e with ethanolic potassium hydroxide effected an internal condensation of the 19a-methyl ketone with the 3-ketone moiety to give 3,10-[2′-oxoethano]-5α-estran-3-ol-17-one (9b). Selective reduction of 9b with lithium tri-*tert*-butoxyaluminum hydride afforded 3,10-[2′-oxoethano]-5α-estran-17-ol (9c). Wolff–Kishner reduction of 9c under forcing conditions gave 3,10-ethano-5α-estrane-3,17-diol (10a) which served as starting material for the synthesis of the 17-substituted 3,10-ethano-5α-estranes. The circular dichroism properties of the 3,10-[2′-oxoethano]-5α-estranes with various 17 substituents were studied. The sign of the Cotton effect can be explained if both the back and front octants are considered.

The literature contains but one report on the synthesis of 3,10-ethanoestranes, and this was by Birch and coworkers.[2] In order to more fully investigate the chemical and physical properties of these steroid derivatives, as well as to study their biological effects, we undertook the synthesis of the parent steroid and several 17-substituted derivatives. The Birch synthesis of 3,10-ethanoestranes, shown in Chart I, was accomplished by first isomerizing 1,4-dihydroestradiol 3-methyl ether (1) to a mixture of 1,4- and 1,2-dihydroestradiol 3-methyl ether (1 and 2), followed by a Diels–Alder reaction on the conjugated diene steroid 2 with methyl vinyl ketone to furnish the ethanoestrane adduct 3.[2]

Our initial synthetic efforts followed the precedent set down by Birch and coworkers.[2] We found that the isomerization of 1 to 2 using Triton B catalyst in dimethyl sulfoxide was superior to the method reported by Birch; however, we were unsuccessful in obtaining

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(2) A. J. Birch and B. McKague, *Aust. J. Chem.*, **23**, 341 (1970).