compounds with mobilities identical to those of *myo*-inositol (II) and 2-deoxy-*myo*-inositol (XXVII). The evidence for the formation of XXVII by demethylation, together with the evidence, already presented, that the oxidized bornesitol solution contains the inosose XXV, indicate that the hydrogenolysis product of R_p 1.04 is L-**2-deoxy-1-*O*-methyl-*myo*-inositol** [(?)-**1-*O*-methyl-*scyllo*-quercitol, XXVI**].[27]

Hydrogenolysis of L-3-Deoxy-1-*O*-methyl-*myo*-inososе-2 (XIV).—The solution of oxidized L-3-deoxy-1-*O*-methyl-*myo*-inositol (XIII) described above was treated by the general hydrogenolysis procedure. Paper chromatography of aliquots of the solution, after removal of the catalyst and the sulfuric acid, showed the presence of XIII and a small amount of material with the mobility of (−)-1-*O*-methylcyclohexane-1,3/2,4-tetrol (XV).

[CONTRIBUTION FROM THE DEPARTMENT OF BIOCHEMISTRY, COLLEGE OF AGRICULTURE, UNIVERSITY OF WISCONSIN, MADISON 6, WIS.]

Cyclitols and Their Methyl Ethers. IV. The Absolute Configurations of the *myo*-Inositol Monomethyl Ethers[1,2]

BY GERALD G. POST AND LAURENS ANDERSON[3]

RECEIVED MAY 17, 1961

(−)-Bornesitol and (+)-ononitol were synthesized by the reduction of inososes derived from quebrachitol (1-*O*-methyl-L-inositol). These syntheses confirm the conclusions of other workers as to the positions of the methyl groups in the bornesitols and ononitols, and establish the absolute configurations of these *myo*-inositol monomethyl ethers. (+)-Bornesitol is D- and (−)-bornesitol is L-1-*O*-methyl-*myo*-inositol; (−)-ononitol is D- and (+)-ononitol is L-4-*O*-methyl-*myo*-inositol.

The task of determining the locations of the methyl groups in the *myo*-inositol monomethyl ethers, *i.e.*, of deciding which of the six possible formulas corresponds to each of the known isomers, was partly accomplished in this Laboratory several years ago.[4] At that time, it was shown that sequoyitol and the synthetic ether of m.p. 212° are the *meso* compounds XI and X, respectively. The remaining four formulas VI–IX, comprising two DL-pairs, are asymmetric, and completion of the task required that these formulas be correctly allocated among the optically active isomers,[5] *viz.*, (+)-bornesitol, (−)-bornesitol, (+)-ononitol and (−)-ononitol. Evidence is now presented which establishes the absolute configurations of these compounds, and thus completes the formula assignments.

When the present work was undertaken, only one effort had been made to determine the positions of the methyl groups in the optically active *O*-methyl-*myo*-inositols. On the basis of a comparison of the electrophoretic mobilities of various cyclitols in borate buffer, Foster and Stacey[6] had concluded that (+)-bornesitol is either VI or VII, *i.e.*, that the bornesitols are the 1-*O*-methyl-*myo*-inositols.[4,7] If this conclusion could be accepted, it followed that the ononitols (not known at the time) would be the 4-*O*-methyl-*myo*-inositols (VIII and IX). However, it seemed important to have a more direct proof,[8] and in any case the experiments in question did not distinguish between enantiomorphs.

Our success in synthesizing sequoyitol by an unequivocal method from a naturally occurring cyclitol of known constitution led us to consider a similar approach to the optically active mono-*O*-methyl-*myo*-inositols. Our attention focused on quebrachitol, a naturally occurring monomethyl ether of L-inositol, for which the formula I had been established.[5] It can be seen (formula I) that there are two, and only two, positions (2 and 3) in quebrachitol at which oxidation followed by reduction in the opposite steric sense will effect a conversion to *myo*-inositol derivatives. It can also be seen that in one case the product will be L-4-*O*-methyl-*myo*-inositol (VIII), and in the other L-1-*O*-methyl-*myo*-inositol (VI); *i.e.*, one of the products must be a bornesitol and the other an ononitol. A further important point is that positions 2 and 3 in quebrachitol are precisely those which were expected to be subject to catalytic oxidation.

As described in the preceding paper[2] quebrachitol was readily oxidized, and an inosose was isolated in good yield from the reaction. The problem of establishing the formula of this inosose was solved in part, and the first of the projected syntheses was accomplished, by reducing the inosose with sodium borohydride. The reduction products were identified as quebrachitol and (−)-bornesitol, showing that the oxidation of quebrachitol had taken place in the predicted way, either at position 3 to give II, or at position 2 to give III. A tentative choice between the two possibilities was made by determining the periodate consumption of the phenylhydrazone of the inosose. Two molar equivalents of the reagent were required, indicating that the oxidation was at position 3 and that the inosose was therefore II [3-*O*-methyl-D-*myo*-inosose-1, 3-*O*-methyl-(−)-*vibo*-inosose]. Corroborating evidence was the fact that one of the products of the hydrogenolysis of the inosose was an *O*-methylquercitol which likewise consumed two molar equivalents of periodate.[2]

(1) Published with the approval of the Director of the Wisconsin Agricultural Experiment Station. This investigation was supported by a research grant (E-385) from the National Institutes of Health, Public Health Service.

(2) Paper III of this series *J. Am. Chem. Soc.*, **84**, 471 (1962).

(3) To whom requests for reprints should be sent.

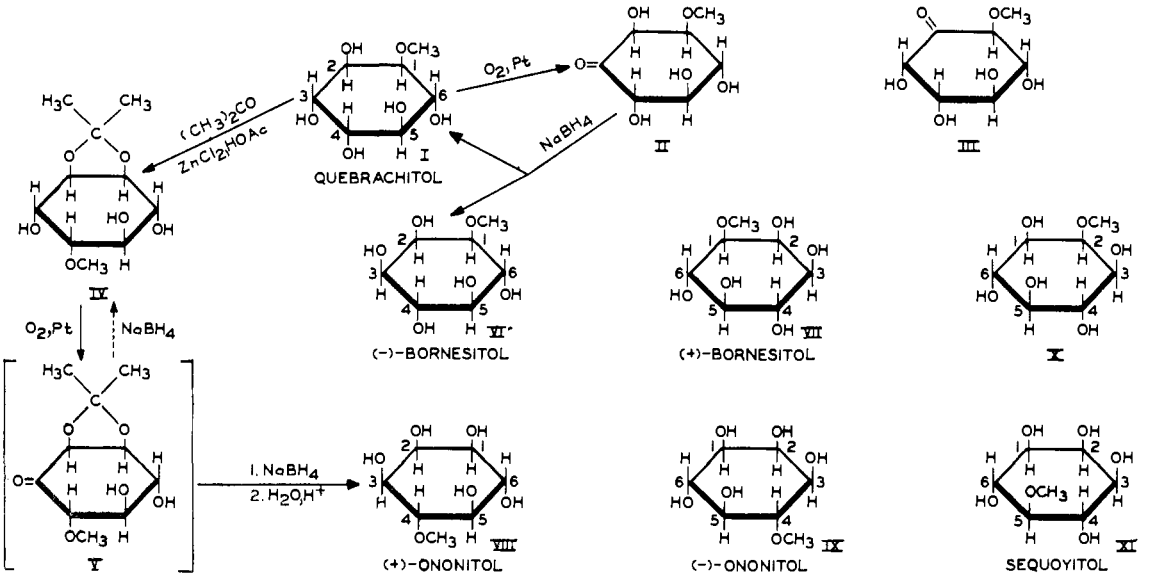
(4) Paper II of this series: L. Anderson, Emily S. DeLuca, A. Bieder and G. G. Post, *J. Am. Chem. Soc.*, **79**, 1171 (1957). The reason for considering the isomerism of the inositol methyl ethers in terms of positions on the ring, and the numbering applicable to the *myo*-derivatives, is discussed in footnotes 4 and 9 of this paper.

(5) S. J. Angyal and L. Anderson, *Adv. Carbohydrate Chem.*, **14**, 135 (1959).

(6) A. B. Foster and M. Stacey, *Chemistry & Industry*, 279 (1953).

(7) For further clarification of the nomenclature see footnote 7 of the preceding paper.

(8) Although the conclusions of Foster and Stacey have been substantiated, the interactions of cyclitols with borate are more complex than these authors supposed; see S. J. Angyal and D. J. McHugh, *J. Chem. Soc.*, 1423 (1957).



However, this evidence was less decisive than that obtained by analysis of the phenylhydrazone, since the quercitol (compound XIII, preceding paper) could conceivably also arise from III.

A suitable starting material for the oxidation at the other desired position was found in *O*-isopropylidenequebrachitol.[9,10] This compound had been shown to have the formula IV, and it thus constituted a derivative blocked at position 3. It was rather inert to the catalytic oxidation, but when the reaction was carried out for a sufficiently long time, appreciable amounts of reducing power appeared in the solution. Reduction of the oxidized solution with sodium borohydride, followed by acid hydrolysis, gave much quebrachitol and a small amount of a *myo*-inositol methyl ether with properties which identified it as (+)-ononitol.

Now, it may be seen that in the case of the inosose from *O*-isopropylidenequebrachitol, the fact that a *myo*-inositol methyl ether is formed by reduction is alone sufficient to fix the location of the oxo group. Of the two positions in quebrachitol at which steric inversion accomplishes a transformation of the compound to a *myo*-inositol ether, only position 2 is available for reaction in the isopropylidene derivative. It follows that oxidation must have taken place there, and hence the inosose formed must be V. Further, V is the isopropylidene derivative of III, and since the *O*-methyl-*myo*-inositol derived from V is an ononitol, the inosose which yields (−)-bornesitol cannot be III. The tentative conclusion that this latter inosose, resulting from the oxidation of unsubstituted quebrachitol, is II is thus confirmed.

The establishment of the structures of the inososes II and V elucidates the absolute configurations of the bornesitols and ononitols. By its derivation from II, (−)-bornesitol must be L-1-*O*-methyl-*myo*-inositol (VI), and the longer known (+)-bornesitol must then be D-1-*O*-methyl-*myo*-inositol (VII). Similarly, its formation from V shows that (+)-ononitol is L-4-*O*-methyl-*myo*-inositol (VIII); (−)-ononitol[11] is D-4-*O*-methyl-*myo*-inositol (IX).

(9) T. Posternak, *Helv. Chim. Acta*, **35**, 50 (1952).

(10) S. J. Angyal and C. G. Macdonald, *J. Chem. Soc.*, 686 (1952).

Corroboration of the conclusions reached here appeared while the work was in progress, and additional confirmation has been published since our preliminary report.[12] Angyal, Gilham and Macdonald,[13] in 1957, obtained (±)-bornesitol by partial demethylation of the dimethyl ether dambonitol, and in view of strong evidence that the latter is 1,3-di-*O*-methyl-*myo*-inositol, concluded that the methyl group is in the 1-position in the bornesitols. These authors also clarified the acyl-migration phenomena associated with an earlier synthesis of (±)-bornesitol from *myo*-inositol 1,3,4,-5,6-pentaacetate.[14] In the same year, Angyal and Gilham[15] reported the synthesis of (±)-ononitol by the action of sodium methoxide on 5,6-anhydro-*allo*-inositol. This synthesis indicated the 4-position for the methyl group in the ononitols. Somewhat later Bien and Ginsburg[16] degraded *O*-isopropylidene-(−)-bornesitol to derivatives of ribitol, and thus showed in an entirely independent way that the bornesitols are the *myo*-inositol 1-methyl ethers. Finally and more recently, Ballou and Pizer[17] have described a synthesis of (+)-bornesitol from galactinol, a naturally occurring *myo*-inositol galactoside. On the basis of this synthesis, which unequivocally establishes the absolute configuration of the product, Ballou and Pizer were led to the formula VII for (+)-bornesitol. The absolute configurations of all of the six possible *myo*-inositol monomethyl ethers may therefore be regarded as firmly established.

Experimental[18]

Periodate Analysis of 3-*O*-Methyl-D-*myo*-inosose-1 Phenylhydrazone.—To 6.88 mg. of the phenylhydrazone[2] was

(11) (−)-Ononitol is known only as a component of racemic ononitol.

(12) L. Anderson and G. G. Post, *Abstracts 134th Natl. Meeting Am. Chem. Soc.*, 13D (1958).

(13) S. J. Angyal, P. T. Gilham and C. G. Macdonald, *J. Chem. Soc.*, 1417 (1957).

(14) L. Anderson and Aurora M. Landel, *J. Am. Chem. Soc.*, **76**, 6130 (1954).

(15) S. J. Angyal and P. T. Gilham, *J. Chem. Soc.*, 3691 (1957).

(16) S. Bien and D. Ginsburg, *ibid.*, 3189 (1958).

(17) C. E. Ballou and L. I. Pizer, *J. Am. Chem. Soc.*, **82**, 3333 (1960).

added 5.00 ml. of 0.05 *M* sodium metaperiodate in 50% methanol. At various times 1-ml. aliquots were analyzed by adding 2 ml. of water, 0.4 ml. of 20% sulfuric acid, 1 ml. of 20% potassium iodide, and titrating the liberated iodine with standard thiosulfate. The periodate uptake in moles per mole of phenylhydrazone at room temperature was: at 0.5 hr., 2.05; at 1.5 hr., 1.96; at 21 hr., 2.09.

(−)-Bornesitol (VI).—Approximately 1.2 g. of sirupy 3-*O*-methyl-D-*myo*-inosose-1 (II), obtained by the chromatography of a solution of oxidized quebrachitol,[2] was dissolved in 20 ml. of water and 0.1 g. of sodium borohydride was added. The solution, which became slightly alkaline (*p*H 8), was allowed to stand at room temperature for 1 hr., after which time it no longer reduced Benedict reagent. The excess sodium borohydride was destroyed with acetic acid and the sodium ions were removed by passing the solution through a Dowex-50 column. Paper chromatography showed the presence of quebrachitol and a compound with the mobility of bornesitol (R_D 0.59), and concentration of the solution precipitated 0.82 g. of material melting from 167–177°. The mother liquors were concentrated to 1 ml. and, together with the crystalline material, chromatographed on a cellulose column with acetone–water 8:1. Two bands were obtained, the first of which yielded 0.61 g. of quebrachitol (I), m.p. 191.5–192°. The second band, on concentration and the addition of ethanol, yielded 0.30 g. of substance melting at 205–205.5° and showing $[\alpha]_D$ −32.6° (*c* 1.0 and 1.4 in water). By comparison, the reported physical constants of (−)-bornesitol are m.p. 203–204° and $[\alpha]_D$ −32° (water),[19] and of (+)-bornesitol m.p. 199–203° and $[\alpha]_D$ +31° (water).[20,21] We found that chromatography (cellulose column) of authentic (+)-bornesitol raised its m.p. to 205–205.5°.

Twenty-three mg. of the material of the second band was refluxed for 1 hr. with 2 ml. of acetic anhydride and 24 mg. of anhydrous sodium acetate. Water was added and the resulting solution concentrated to give a white precipitate weighing 27.3 mg., m.p. 140°; reported for (−)-bornesitol pentaacetate,[19] m.p. 142°, 157°; for (+)-bornesitol pentaacetate,[21] m.p. 138–139°, 157°; the acetates are dimorphic. The infrared spectrum (chloroform solution) was essentially identical with that of an authentic sample of (+)-bornesitol pentaacetate.

Further confirmation that the material of band 2 was (−)-bornesitol was obtained by demethylating it to *myo*-inositol, identified by m.p., mixed m.p., chromatographic mobility and conversion to the hexaacetate.

(+)-Ononitol (VIII).—One gram of *O*-isopropylidene-quebrachitol (IV), prepared by the procedure of Angyal and Macdonald,[10] was treated for 44.5 hours with oxygen over platinum (procedure B, preceding paper). The product, 2,3-*O*-isopropylidene-6-*O*-methyl-D-*myo*-inosose-1 [2,3-*O*-isopropylidene-6-*O*-methyl-(−)-*vibo*-inosose, V], was not isolated. Instead, the oxidized solution was filtered, 104 mg. of sodium borohydride was added, and the solution was allowed to stand at room temperature for 2 hr. The excess reducing agent was destroyed with acetic acid and the sodium ions removed with Dowex - 50 (H^+). The concentration of acetic acid was increased to approximately 10% and the solution was refluxed for 10 minutes, after which the acetic acid and boric acid were removed by repeated concentrations and additions of water and methanol. The products were then separated by cellulose column chromatography with acetone–water 9:1. The major product consisted of 0.50 g. of quebrachitol (I), m.p. 190–191°.

After the quebrachitol was eluted, an additional band was detected. This band contained 40 mg. of material which crystallized from aqueous ethanol as a hydrate, m.p. 167–168°. Heating the substance overnight *in vacuo* at 100° caused the loss of one molar portion of water, but did not change the melting point; $[\alpha]_D^{23}$ (anhydrous basis) +5.5° (*c* 11.2, water); reported[19] for (+)-ononitol are m.p. 172° and $[\alpha]_D$ +6.6° (water).

The synthetic methyl ether was acetylated by refluxing 22 mg. of it with 3 ml. of acetic anhydride and 25 mg. of anhydrous sodium acetate for 0.5 hour. After cooling, water was added and on concentration 24.3 mg. of crystals precipitated. The melting point was 121°, $[\alpha]_D^{23}$ −11.14° (*c* 0.83, $CHCl_3$); lit.[19] for (+)-ononitol pentaacetate: m.p.'s 122°, 131° (dimorphic), $[\alpha]_D$ −12° ($CHCl_3$).

On demethylation with refluxing HI, the synthetic ononitol yielded *myo*-inositol, identified by m.p., mixed m.p., chromatographic mobility and conversion to the hexaacetate.

(18) For general statements pertaining to experimental procedure, and for the methods used for paper chromatography, cellulose column chromatography, demethylation and catalytic oxidation, see the relevant paragraphs of the Experimental section of the preceding paper.

(19) V. Plouvier, *Compt. rend.*, **241**, 983 (1955).

(20) E. R. Flint and B. Tollens, *Ann.*, **272**, 288 (1893).

(21) F. E. King and L. Jurd, *J. Chem. Soc.*, 1192 (1953); our authentic sample was from Prof. King.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE UNIVERSITY OF MICHIGAN, ANN ARBOR, MICH.]

Kinetic Evidence for the Formation of Azene (Electron-deficient Nitrogen) Intermediates from Aryl Azides[1]

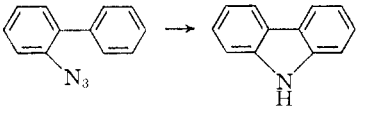
BY PETER A. S. SMITH AND J. HERBERT HALL

RECEIVED JULY 11, 1961

The kinetics of the thermal decomposition of a group of phenyl and 2-biphenylyl azides bearing halogen, nitro, methyl or methoxy substituents have been measured at several temperatures and in different solvents. The variation of rate with substitution is small; the enthalpies and entropies of activation show a linear relation. None of these functions can be correlated satisfactorily by the Hammett equation; *m*-substituents have little effect on the activation enthalpies, but *p*-substituents have an effect that follows the order of the values of $\Delta\sigma$ ($= \sigma p - \sigma m$). There is little effect of solvent on the rates other than a weak acceleration by hydroxylic solvents. The over-all behavior is best accounted for by initial cleavage to an aryl azene intermediate, Ar–N:

The thermal decomposition of azides usually leads to the loss of two-thirds of the azide nitrogen and the formation of products derived from rearrangement (eq. 1), cyclization (eq. 2) or hydrogen abstraction (eq. 3).[2] These results may be interpreted as coming about by a concerted reaction path, by initial formation of an adduct, such as a triazoline or triazene, or by initial formation of an azene,[3] R–N: Many attempts have been made to inter-

$$R_3C{-}N_3 \longrightarrow R_2C{=}N{-}R + N_2 \quad (1)$$



$$+ N_2 \quad (2)$$

$$Ar{-}N_3 \xrightarrow{(H)} Ar{-}NH_2 + N_2 \quad (3)$$

(1) From the doctoral thesis of J. H. H. Supported in part by the Office of Ordnance Research, U. S. Army.

(2) J. H. Boyer and F. C. Canter, *Chem. Rev.*, **54**, 1 (1954).

(3) The term "azene" is used in this paper to denote derivatives of NH, also known as "imine radical" and "univalent nitrogen." The shorter term, apparently introduced by Huisgen, has obvious advantages. The word "nitrene," seen occasionally in recent literature, is inadmissible, inasmuch as it has long been the accepted term for the ylides of Schiff's bases (*cf. C. A.*, Decennial Indices).