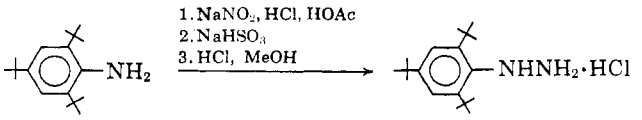
III

For the synthesis, the already known 2,4,6-tri-*t*-butylaniline (II) was prepared and diazotized. The diazonium salt was reduced with freshly prepared sodium bisulfite (eq. 1). The product I was obtained



II I·HCl (1)

as an oil. With hydrochloric acid, however, it formed a crystalline salt with limited solubility in aqueous methanol, which gave a correct elemental analysis.

During the preparation of II, we found it convenient to nitrate a mixture of 1,3,5-tri-*t*-butylbenzene and 1,4-di-*t*-butylbenzene, obtained by *t*-butylation of benzene. These two hydrocarbons have similar melting points, boiling points, and solubilities and are difficult to separate, except by use of an efficient fractionating column[1] or by preparative gas–liquid chromatography.[3] The 1,3,5-tri-*t*-butylbenzene was nitrated preferentially, however, in spite of its having fewer available positions and more steric hindrance for nitration than 1,4-di-*t*-butylbenzene. These factors are more than offset by accumulation of the activating influences of the *t*-butyl groups. The result is consistent with calculations based on data for *t*-butylbenzene, which indicate that 1,3,5-tri-*t*-butylbenzene would be nitrated about 80 times as rapidly as 1,4-di-*t*-butylbenzene.[4]

2,4,6-Tri-*t*-butylphenylhydrazine was found to have a pK_a of 3.66 in 50% ethanol at 30° and to be a weaker base than phenylhydrazine by about 1.4 pK units under these conditions. The result is discussed in detail elsewhere.[5] It is believed that a base-weakening effect of steric hindrance to hydration more than offsets base-strengthening inductive effects of the *t*-butyl groups and, possibly, a base-strengthening steric inhibition of resonance.

Experimental Section

2,4,6-Tri-*t*-butylaniline (II) was prepared as described by Bartlett, Roha, and Stiles[1a], except that we found it was possible and convenient to obtain 2,4,6-tri-*t*-butylnitrobenzene by nitration of the difficultly separable mixture of 1,3,5-tri-*t*-butylbenzene and 1,3- and 1,4-di-*t*-butylbenzene obtained by alkylation of benzene (1 mole) with *t*-butyl chloride (2.1 moles) and aluminum chloride (1.1 mole) in carbon disulfide as a solvent. A semisolid fraction boiling at 118–135° at 12 mm. was filtered with suction, and 11.2 g. of the solid was dissolved in 8 ml. of acetic acid and 6 ml. of acetic anhydride. The mixture was cooled in an ice–salt bath, and 1.6 g. of fuming nitric acid was added dropwise at 0°. The solid product precipitated from the reaction mixture with each addition of nitric acid. After 1 hr. of standing, the mixture was filtered with suction and the crude product was recrystallized from petroleum ether (b.p. 30–60°): yield 3.4 g., m.p. 198–200°.

Reduction of 2,4,6-tri-*t*-butylnitrobenzene with sodium amalgam and methanol[1a] gave II contaminated with sodium carbonate. The II was readily purified, however, by crystallization from methanol–acetic acid: m.p. 143.5–144.5°.

2,4,6-Tri-*t*-butylphenylhydrazine (I).—To a mixture of 5 g. of II, 50 ml. of glacial acetic acid, and 13 ml. of concentrated hydrochloric acid, cooled to 0°, there was added with stirring a precooled solution of 1.3 g. of sodium nitrite in 7 ml. of water. A yellow precipitate was observed. To the mixture was then added a solution of sodium bisulfite, freshly prepared from 4 g. of sodium hydroxide in 30 ml. of water and sulfur dioxide to a phenolphthalein end point.[6] The mixture was heated at reflux overnight, cooled, and made basic with sodium hydroxide. An oil separated and was extracted into ether. After efforts to crystallize the product failed, it was converted to a solid hydrochloride by treatment with a small amount of 4 *M* hydrochloric acid in methanol solution, and the solid was purified by recrystallization from aqueous methanol: m.p. 208–210° dec.

Anal..[7] Calcd. for $C_{18}H_{33}ClN_2$: C, 69.09; H, 10.63; N, 8.95. Found: C, 69.49; H, 10.63; N, 8.87.

For determination of its pK_a, a solution of 0.1405 g. of the hydrochloride in 20 ml. of 50% aqueous ethanol was titrated with a 0.104 *N* solution of carbonate-free sodium hydroxide in 50% ethanol at 30°. A Beckman Model H2 pH meter was used with a glass electrode and calomel half-cell. The pH at the point of half-neutralization was 3.68. A correction for hydrolysis amounts to −0.02 pK unit. When freshly prepared phenylhydrazine hydrochloride was titrated under similar conditions (50% ethanol), but at 27°, its pK_a was found to be 5.09. A correction for the activity coefficient of the hydrazinium ion may amount to about −0.15 pK unit in each case,[8] but was not applied.

Acknowledgment.—We are indebted to Dr. J. L. Goldberg for use of a pH meter and advice on its operation and to the Research Committee of The City College for a grant-in-aid.

(3) G. A. Olah, C. G. Carlson, and J. C. Lapiere, *J. Org. Chem.*, **29**, 2687 (1964).

(4) The calculations follow. *t*-butylbenzene is nitrated 15.7 times as rapidly as benzene, and the product is 12.0% *o*-, 8.5% *m*-, and 79.5% *p*-nitro-*t*-butylbenzene [H. Cohn, E. D. Hughes, M. H. Jones, and M. G. Peeling, *Nature*, **169**, 291 (1952)]. The partial rate factors (rates relative to that for any one position in benzene) are therefore *ortho* 5.6, *meta* 4.0, and *para* 75. For each position in 1,3,5-tri-*t*-butylbenzene, a partial rate factor may be calculated as a product of partial rate factors, one relating to each substituent and its position [F. E. Condon, *J. Am. Chem. Soc.*, **70**, 1963 (1948)]; that is $75 \times 5.6 \times 5.6 = 2350$. The rate for the molecule as a whole would be $3 \times 2350 = 7050$, relative to that for any one position in benzene. Similarly, the relative rate of nitration of 1,4-di-*t*-butylbenzene is calculated as $4 \times 4.0 \times 5.6 = 89.6$, and that for 1,3-di-*t*-butylbenzene is 887. The rate of nitration of 1,3,5-tri-*t*-butylbenzene therefore is estimated to be about 80 times that of 1,4-di-*t*-butylbenzene and about 8 times that of 1,3-di-*t*-butylbenzene (a minor component of the mixture nitrated.)

(5) F. E. Condon, *J. Am. Chem. Soc.*, **87**, 4491 (1965).

(6) H. Gilman, "Organic Syntheses," Coll. Vol. I, John Wiley and Sons, Inc., New York, N. Y., 1941, p. 443.

(7) Analysis were by Carl Tiedcke Laboratory of Microchemistry, Teaneck, N. J.

(8) See J. Kielland, *J. Am. Chem. Soc.*, **59**, 1675 (1937), and available data for hydrazine: G. Schwartzenbach, *Helv. Chim. Acta*, **19**, 178 (1936); N. Yui, *Bull. Inst. Phys. Chem. Res.* (Tokyo), **20**, 256 (1941); *Chem. Abstr.*, **35**, 4660 (1941); R. L. Hinman, *J. Org. Chem.*, **23**, 1587 (1958).

The Absolute Configuration of Thujopsene[1]

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Thujopsene, a tricyclic sesquiterpene, has been shown to be a constituent of the wood oil and heartwood of many genera belonging to the natural order Cupressales.[3] In the past few years the chemistry of

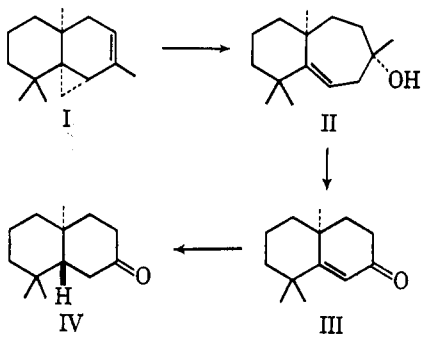
(1) This work was supported in part by Grant GP-3890, National Science Foundation.

(2) Roche Anniversary Foundation Postdoctoral Fellow, 1963–1965.

(3) For a summary of the numerous isolations of thujopsene, see T. Norin, *Acta Chem. Scand.*, **15**, 1676 (1961).

this widely occurring hydrocarbon has been extensively investigated and it has been shown that the compound possesses the gross structure I.[3-8] The *cis* steric relationship between the angular methyl group and the cyclopropane ring has been established both by a stereospecific synthesis[9] and by chemical evidence from a series of degradative experiments.[10]

Prior to the determination of the relative stereochemistry of thujopsene, the absolute configuration of the material was assigned on the basis of optical rotatory dispersion of ketones related to it.[11] In this latter work, thujopsene (I) was transformed into widdrol (II), a transformation which has been shown



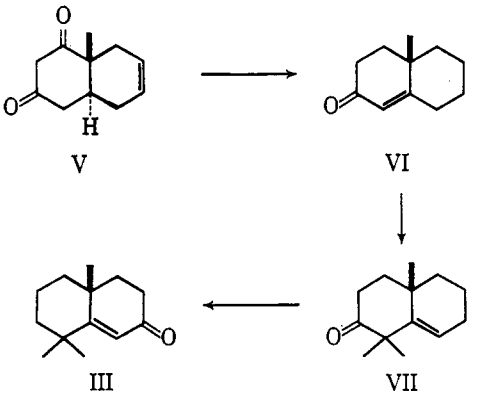
I II IV III

not to involve the angular methyl group.[12] Widdrol, in turn, was degraded in four steps to 8,8,10-trimethyl-$\Delta^{1(9)}$-2-octalone (III). The O.R.D. curve of the octalone III exhibited a strong positive Cotton effect. Since 3β-acetoxy-4,4-dimethyl-Δ^5-cholesten-7-one and related derivatives of Δ^5-lanostene all gave rise to negative Cotton curves,[13] it was inferred[11] that the orientation of the angular methyl group in the trimethyloctalone III was opposite to that of the C-10 angular methyl group in a steroid, and therefore α in the absolute sense. The O.R.D. of the saturated ketone IV derived from III was in agreement with this conclusion.

This assignment of absolute stereochemistry based upon the O.R.D. of an unsaturated ketone and its related saturated ketone mixture produced by chemical reduction warrants evaluation. With regard to the O.R.D. of the unsaturated ketone III, it has recently been shown[14] that, in contrast to the situation among saturated ketones, such a measurement should be used only with great caution for absolute configurational assignment and used only in those instances where the conformational relationship between the reference substance and the unknown compound is unambiguous. It has to be considered that steroids which have two additional fused rings may have ring A in a different conformation from that of the related octalone. Such a conformational change can lead to a change in the sign of the O.R.D. curve.

With regard to the saturated ketone IV prepared by the lithium–ammonia reduction of the unsaturated ketone III, the earlier worker[11] assumed the predominance of the *trans* isomer. Attention must be directed to the stereochemical result of such a reaction since it has recently been shown[15] that such a reduction is not thermodynamically controlled. Any *cis* isomer of IV present in the reduction mixture could exist in a "twist" conformation and thus contribute strongly to the O.R.D. of a *cis–trans* mixture.[16,17] Furthermore, a twist conformation of the *cis* isomer would contribute to the O.R.D. curve in the same manner as the *trans* isomer. Thus, also in this reaction sequence, caution must be exerted before conclusions regarding absolute configurations are formed.

In order to establish with certainty the absolute configuration of the trimethyloctalone III, the compound was synthesized from a starting material known to possess the absolute configuration of the natural steroids. (−)-*trans*-10β-Methyl-Δ^6-octalin-1,3-dione (V)[18] was converted to the desired octalone III *via* 10β-methyl-$\Delta^{1(9)}$-octalin-2-one (VI) and 1,1,10-trimethyl-Δ^8-octalin-2-one (VII) following published procedures.[9,19,20] The O.R.D. curve of the optically active synthetic product III showed a negative Cotton effect. Since the octalone III from widdrol gave rise to a positive Cotton effect, its absolute configuration must be the mirror image of the synthetic material which possesses the absolute configuration of the steroids. This result confirms the earlier assigned absolute configuration of thujopsene.



V VI III VII

Experimental Section

(−)-*trans*-**2-Methoxy-10β-methyl-$\Delta^{2,6}$-hexalin-4-one.**—Following the given procedure of Speziale, Stephen, and Thompson,[19] (−)-*trans*-10β-methyl-Δ^6-octalin-1,3-dione (V), m.p. 161–174° (lit.[19] m.p. 187–189°), was converted into its enol methyl ether, m.p. 86.5–91.0°, $[\alpha]^{25}D$ −72° (*c* 3.3, $CHCl_3$) [lit.[19] m.p. 91–92°, $[\alpha]D$ −59° (*c* 2.0, $CHCl_3$)].

(+)-*trans*-**10β-Methyldecalin-2-one.**—Following the published procedure,[19] the above (−)-enol methyl ether was reduced with

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(9) W. G. Dauben and A. C. Ashcraft, *J. Am. Chem. Soc.*, **85**, 3673 (1963).
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(11) C. Enzell, *ibid.*, **16**, 1553 (1962).
(12) W. G. Dauben and L. E. Friedrich, *Tetrahedron Letters*, 2675 (1964).
(13) C. Djerassi, C. Halpern, V. Halpern, and B. Riniker, *J. Am. Chem. Soc.*, **80**, 4001 (1958).
(14) C. Djerassi and J. E. Gurst, *ibid.*, **86**, 1755 (1964).
(15) G. Stork and S. D. Darling, *ibid.*, **86**, 1761 (1964).
(16) W. G. Dauben, R. M. Coates, N. D. Vietmeyer, L. J. Durham, and C. Djerassi, *Experientia*, in press.
(17) C. Djerassi and W. Klyne, *Proc. Natl. Acad. Sci. U. S.*, **48**, 1093 (1962).
(18) We are indebted to Dr. A. J. Speziale of the Agricultural Research Branch, The Monsanto Chemical Co., St. Louis, Mo., for a generous gift of this compound.
(19) A. J. Speziale, J. A. Stephens, and Q. E. Thompson, *J. Am. Chem. Soc.*, **76**, 5011 (1954).
(20) C. Djerassi and D. Marshall, *ibid.*, **80**, 3986 (1958). These workers employed the opposite antipode to the one used in the present work.

lithium aluminum hydride to the 4-hydroxy derivative which, in turn, was hydrolyzed and dehydrated to yield (−)-*trans*-10β-methyl-$\Delta^{3,6}$-hexalin-2-one. The crude product was hydrogenated over platinum according to the procedure of Djerassi and Marshall[20] to yield (+)-*trans*-10β-methyldecalin-2-one (92% pure by v.p.c.), $[\alpha]^{25}D$ +40° (*c* 2.0, $CHCl_3$) [lit.[21] $[\alpha]D$ +33° (*c* 1.14, $CHCl_3$)].

(+)-10β-Methyl-$\Delta^{1(9)}$-octalin-2-one (VI).—The 92% pure, optically active decalone was brominated following the method used for its antipode[20] and (+)-*trans*-3-bromo-10β-methyldecalin-2-one was obtained as colorless needles after recrystallization from aqueous acetone: m.p. 135.0–136.5°, $[\alpha]^{25}D$ +18° (*c* 2.0, $CHCl_3$) [for antipode lit.[20] m.p. 137–139°, $[\alpha]D$ −21° ($CHCl_3$)]. The bromo ketone was dehydrobrominated with collidine and the mixture of Δ^3- and $\Delta^{1(9)}$-enones was separated by the procedure of Djerassi and Marshall.[20] The crude $\Delta^{1(9)}$-enone was used directly in the next reaction.

(−)-8,8,10β-Trimethyl-$\Delta^{1(9)}$-octalin-2-one (III).—The above $\Delta^{1(9)}$-enone was methylated, reduced, and then oxidized according to the published procedures[9] and the product was distilled, b.p. 119–120° (0.3 mm.) [lit.[9] b.p. 129–130° (10 mm.)]. V.p.c. analysis, in comparison with optically inactive material, showed the product to be more than 95% pure. Professor C. Djerassi kindly determined the O.R.D. curve of this material in methanol (*c* 0.12) at 25°: $[\theta]_{589}$ −115°, $[\theta]_{353}$ −2580°, $[\theta]_{300}$ +3920°, $[\theta]_{294}$ +3850°.

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Methyl 2,6-Anhydro-3,4-di-*O*-methyl-α-D-mannoside. An Intramolecular Nucleophilic Displacement of Mesylate with Inversion

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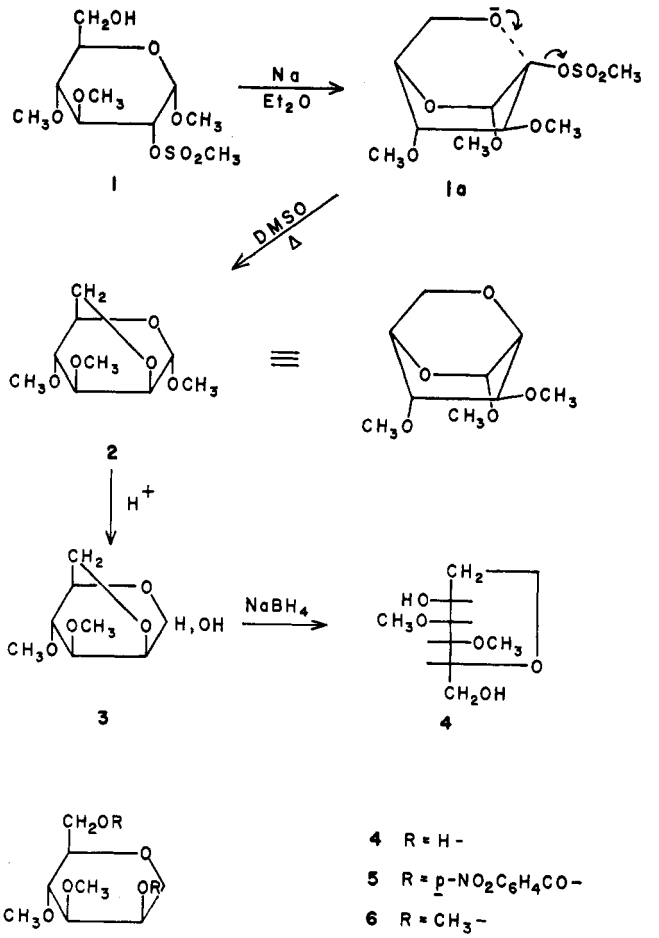
Recent publications from this laboratory have described reactions of carbohydrate mesyloxy groups with various nucleophilic reagents.[2,3] Reaction of methyl 2-*O*-mesyl-3,4,6-tri-*O*-methyl-α-D-glucoside with aqueous sodium hydroxide,[2] methanolic sodium methoxide, or sodium methoxide in dimethyl sulfoxide (DMSO)[3] gave only products resulting from nucleophilic attack at sulfur in the mesyloxy group. No evidence for nucleophilic displacement of the mesyloxy group, involving Walden inversion, could be detected.

Selective demesylation of methyl 2,6-di-*O*-mesyl-3,4-di-*O*-methyl-α-D-glucoside[4] made available methyl 2-*O*-mesyl-3,4-di-*O*-methyl-α-D-glucoside (**1**) and it was postulated that this compound might be induced to undergo an intramolecular displacement of the mesyloxy group resulting in a new 2,6-anhydro sugar.

Treatment of **1** with excess sodium methoxide in refluxing anhydrous methanol failed to show any reaction. When **1** was treated with 1.1 equiv. of potassium *t*-butoxide in anhydrous DMSO at 70°, thin layer chromatography indicated a slow reaction and the formation of a small amount of a compound running faster than **1**. After 20 hr. the mixture contained a small amount of this product together with a large amount of unchanged starting material and some methyl 3,4-di-*O*-methyl-α-D-glucoside.

CHART I



4 R = H-
5 R = p-NO2C6H4CO-
6 R = CH3-

To decrease demesylation due to intermolecular reaction with alkoxide ion, the 6-sodio salt was prepared by treatment of **1** with sodium in ether and the condensation was carried out at 85° at high dilution in DMSO.

The fast-running product was isolated by ether extraction and column chromatography as a clear sirup which crystallized after distillation. This compound was shown to be the expected methyl 2,6-anhydro-3,4-di-*O*-methyl-α-D-mannoside (**2**) by a series of reactions which ruptured the 1,5 ring and left the 2,6 ring intact (see Chart I). Mild acid hydrolysis removed the glycosidic methyl group and the resulting 2,6-anhydro-D-mannose derivative **3** was reduced with sodium borohydride to an anhydrohexitol derivative, 2,6-anhydro-3,4-di-*O*-methyl-D-mannitol, preferably called 1,5-anhydro-3,4-di-*O*-methyl-D-mannitol (**4**). This compound crystallized and also gave a crystalline di-*p*-nitrobenzoate (**5**).

Methylation of **4** gave a tetramethyl derivative which was shown to be 1,5-anhydro-2,3,4,6-tetra-*O*-methyl-D-mannitol (**6**) by comparison of its physical properties with those of an authentic sample prepared by methylation of styracitol (1,5-anhydro-D-mannitol).

The only previously reported 2,6-anhydro sugar derivative, methyl 2,6-anhydro-α-D-altrose, was prepared by Rosenfeld, Richtmeyer, and Hudson.[5]

(1) National Academy of Sciences–National Research Council Visiting Scientist Resident Research Associate.

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