proceeds through the first excited triplet state of diphenylacetylene.[15]

Experimental Section

The melting point is uncorrected. The nmr spectrum was measured in CCl_4 on a Varian DP-60-IL instrument. The infrared spectrum was obtained on a Perkin-Elmer Model 614 spectrophotometer. The uv spectrum was recorded on a Carey Model 11 spectrophotometer.

7,8-Diphenyl-2-oxabicyclo[4.2.0]oct-7-ene.—Diphenylacetylene (2.0 g, 0.11 mol) was dissolved in 80 g (0.98 mol) of 2,3-dihydropyran and irradiated in quartz for 24 hr at 2537 Å in a Rayonet photochemical reactor while exposed to the atmosphere. Only one reaction product and no diphenylacetylene could be detected by glpc after this time. The reaction mixture was freeze dried and the residual syrup was recrystallized from a methanol–water solution to give 2.12 g (81.5% based on reacted diphenylacetylene) of a white crystalline 1:1 adduct: mp 56–58°; ir (CCl_4), 3040 (aromatic C—H), 2920 (aliphatic C—H), 1585 (aromatic C=C), and 1100 cm^{-1} (C—O—C); uv (cyclohexane), λ_{max} 298 mμ; nmr (CCl_4), τ 2.75 (10 H, multiplet, aromatic protons), 5.40 (1 H, doublet, $J_{1,6}$ = 4.5 cps, H_1), 6.24 (2 H, multiplet, H_3 and $H_{3'}$), 6.90 (1 H, quartet, $J_{5',6}$ = 10.5 cps, H_6), and 8.40 (4 H, multiplet, H_4, $H_{4'}$, H_5, and $H_{5'}$).

Anal. Calcd for $C_{19}H_{18}O$: C, 86.43; H, 6.91. Found: C, 86.05; H, 7.07.

Registry No.—Diphenylacetylene, 501-65-5; 2,3-dihydropyran, 110-87-2; I, 15895-76-8.

(15) There is evidence that the presence of oxygen is required for efficient generation of the triplet state of diphenylacetylene in the absence of sensitizer. See R. C. Henson and E. D. Owen, *Chem. Commun.*, 153 (1967).

The Synthesis of 2- and 4-Bromoestradiol[1]

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Since the 2 and 4 isomers of bromoestradiol (2- and 4-bromo-1,3,5(10)-estratriene-3,17β-diol) were of interest in the cancer program of the Cancer Chemotherapy National Service Center of the National Institutes of Health,[1] they were synthesized in this laboratory. The identity and purity of 4-bromoestradiol is of more than usual importance since it has served as a standard for analyses of microquantities of steroids in biological materials and as a model for X-ray crystallographic studies for Fourier analyses.[2,3] These latter data have, in turn, been used for the elucidation of structures such as that of the plant estrogen mirestrol,[4] as well as for calculations of electronic charge densities related to studies of interactions between steroids and proteins in biological systems.[5,6]

Slaunwhite and Neely[2] have reported methods for the selective preparation of the 2- or 4-bromo isomers of estrone and estradiol with bromine in the presence of iron powder in high yields (75–90%) and purity. We were unable to confirm these results and repeatedly obtained intractable mixtures from which only minor amounts of monobromo isomers were isolated. The formation of the 2 isomer is described by these authors as particularly sensitive to subtle factors, such as the source of the bromine used, etc.[7] They also prepared 4-bromoestradiol by an alternate method in 85% yield, treating estradiol with N-bromosuccinimide in refluxing carbon tetrachloride. In our hands only 7.5% was thus obtained and our physical constants differed greatly from theirs. Subsequently we used the procedure described below, obtaining yields of 25–40% of pure 4-bromoestradiol by treating estradiol with an equimolar amount of N-bromoacetamide in ethanol at 25°. These conditions correspond to those used by Woodward[8] or by Schwenk and coworkers[9] for the preparation of 2,4-dibromestradiol or 4-bromoestrone, respectively. However, no 2-bromo isomers were isolated by these authors, a point stressed by Schwenk and coworkers. From consideration of electronic and steric effects there is, on the balance, no obvious reason for such discrimination, if this is an electrophilic substitution reaction by a bromonium ion. This is illustrated by the fact that nitration of estrone with nitric acid give about equal yields of the 2- and the 4-nitroestrone (37 and 40%, respectively).[10] We therefore carefully examined the mother liquor from the preparation of the 4-bromoestradiol for the presence of the 2 isomer. Guided by thin layer chromatography a product was isolated which upon purification proved to be the 2-bromoestradiol, although its physical characteristics differed markedly from those reported before.[2] Chromatography of its diacetate (V) and fractional precipitation from a solution of its sodium salt removed a very persistent impurity (2,4-dibromoestradiol). The final yield of analytically pure 2-bromoestradiol was usually only about 5.5%, primarily because of high losses during the purification procedure. The 4-bromo isomer was more easily separated, owing to its relatively low solubility, in yields of 25–40%. The indications are, judging from crude yields, thin layer chromatograms and nuclear magnetic resonance data, that in fact the 2 and the 4 isomer are formed in an almost equal ratio (about 3:4). Thus, at least in this particular halogenation of a phenolic steroid no *ortho* position appears to be preferred over the other, contrary to earlier reports.[9]

As mentioned briefly there are substantial differences between our physical data and earlier ones,[2] in fact some identities are clearly in doubt.[11] The various

(1) Supported by Contract No. PH-43-62-479, Cancer Chemotherapy National Service Center, National Institutes of Health, U. S. Public Health Service.

(2) W. R. Slaunwhite and L. Neely, *J. Org. Chem.*, **27**, 1749 (1962).

(3) D. A. Norton, G. N. Kartha, and C. T. Lu, *Acta Cryst.*, **16**, 89 (1963); **17**, 77 (1964); also *Biophys. J.*, **5**, 425 (1965).

(4) N. E. Taylor, D. Crowfoot Hodgkin, and J. S. Rollett, *J. Chem. Soc.*, 3685 (1960).

(5) K. Saudaram and R. K. Mishra, *Biochem. Biophys. Acta*, **94**, 601 (1965).

(6) Both 2- and 4-bromoestradiol were found inactive in estrogen and antiimplantation tests performed in the laboratories of Drs. J. R. Brooks and D. J. Patanelli of the Merck Institute for Therapeutic Research, Rahway, N. J. Such negations of hormonal activities are interesting and possibly of value in the field of cancer. No information has as yet been received by us from the National Institute of Health.

(7) We tried in vain various brands of bromine since the one used by the authors was no longer available. Electrolytically reduced "Iron, Reagent, Powder" from Matheson Coleman and Bell was used by us, the quality and dispersion of which could influence the results.

(8) R. B. Woodward, *J. Amer. Chem. Soc.*, **62**, 1625 (1940).

(9) E. Schwenk, C. C. Castle, and E. Joachim, *J. Org. Chem.*, **28**, 136 (1963).

(10) T. Utne, R. B. Jobson, and R. D. Babson, *ibid.*, in press.

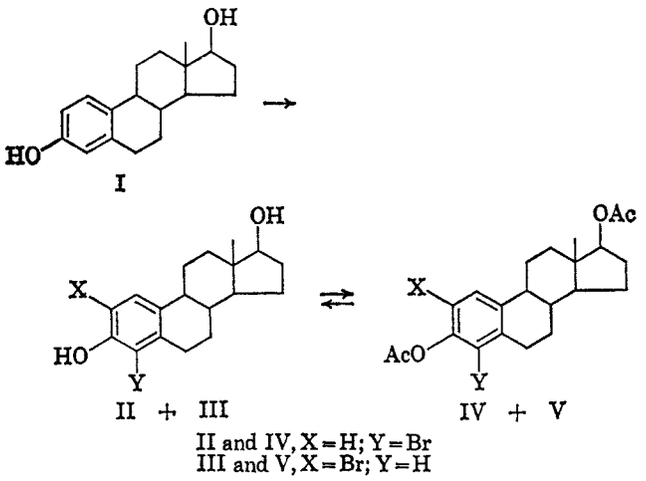
(11) A recent example of a difference between molecular bromine and N-bromoacetamide in aromatic substitution reactions as to isomers formed has been presented by S. Gronowitz, N. Gjös, R. M. Kellog, and H. Wynberg, *ibid.*, **32**, 463 (1967).

TABLE I

	Mp, °C	$[\alpha]^{25}D$, deg	λ_{max}, mμ	ε
2-Bromoestradiol (III)				
Ref 12	197–198	+104	287 (292)	3440 (3230)
Ref 2	156–157	+132	281	2320
Diacetate (V)				
Ref 12	166–168	+41	282.5, 275	1490, 1270
Ref 2	162–163	+109	269	530
4-Bromoestradiol (II)				
Ref 12	213.5–215	+43	283, 288	2220, 2200
Ref 2	207–208	+129	283	2240
Diacetate (IV)				
Ref 12	175.5–177.5	+25	269, 277	466, 440
Ref 2	143–144	+103	275	1280
4-Bromoestrone				
Ref 2	264–265	+136	281	2170
Ref 9	281–283	+147	282, 299	2234, 2340
2,4-Dibromoestrone				
Ref 2	225–226	+133	291 (285)	2800
Ref 9	235–237	+63	285, 293	2900, 3206
2,4-Dibromoestradiol				
Ref 2	218–219	+122	291 (286)	2850
Ref 12	223–226	+66	292 (287)	2800

constants are summarized in Table I,[2,9,12] together with some pertinent data from the literature, which seem to support our values. Of particular note are the differences in melting points and ultraviolet intensities for the 2-bromoestradiol and the strong additional ultraviolet maximum for the 4-bromoestradiol (at 288 mμ) as well as the large differences in optical rotations (up to as much as 86°). Our bromo isomers were both inert toward alcoholic silver nitrate at 25° over 2 days and toward alcoholic potassium hydroxide at 25° for 3 hr, indicating that the bromine atoms were indeed on the aromatic ring.[8] Elsewhere[10] it has been pointed out that in a series of 2- and 4-substituted 1,3,5(10)-estratrienes the ultraviolet absorption intensities enable a facile differentiation of the isomers, since those of the 2 isomers were consistently higher than those of the 4 isomers, mostly by a factor of two to four. As seen above this is also the case for our 2- and 4-bromoestradiol, although the ratio of intensities at 1.56 is somewhat lower than usual, whereas for the corresponding diacetates the ratio is 2.9. Previously equal intensities were reported[2] for these isomers (ratio 1.04), whereas for the diacetates the ratio was actually reversed (0.41). Ultraviolet data similar to ours were found for small samples prepared *via* a Sandmeyer reaction on the 2- and the 4-aminoestrone methyl ether,[2,13,14] followed by cleavage of the ether and sodium borohydride reduction of the ketone. This longer route was less suited for preparative work owing to the small over-all yields.

Despite these unexplainable differences, we believe that our products are pure and of the assigned structures, based on data from thin layer chromatography, phase solubility analyses, nuclear magnetic resonance data, infrared or ultraviolet spectra, elemental analyses, and chemical behavior. (Vapor phase chromatography failed to separate the 2- and 4-bromo isomers.) The nmr spectra clearly indicate the structures to be as formulated below. In one case a quartet centered at τ 2.82 (J = 8.8 cps) is attributed to the *ortho* protons of the 4-bromoestradiol (II), whereas a pair of singlets



at 2.39 and 2.97, without discernible splitting of the *para* protons, is consistent with the 2-bromoestradiol (III) structure.

Experimental Section

Melting points were taken on a calibrated Thomas–Hoover Unimelt apparatus. Ultraviolet spectra were run on a Cary 11 spectrophotometer, infrared spectra were run on a Perkin-Elmer 421 grating spectrophotometer, and nmr spectra were determined on a Varian A-60 spectrometer. Chemical shifts are reported in τ values relative to tetramethylsilane. Optical rotations were measured on a Zeiss photoelectic precision polarimeter.

4-Bromoestradiol (II).—Pure N-bromoacetamide (recrystallized from chloroform–hexane) (20 g, 0.145 mol) was added in portions over 1 hr at 25° to a stirred solution of 40 g of estradiol (I, 0.147 mol) in 2 l. of ethanol dried over molecular sieves. A crystalline material was filtered off after 3 hr and the mother liquor chilled to 0° to give a total of 25 g of crude 4-bromoestradiol. A solution of this product in 500 ml of hot chloroform was poured onto a 900-g silica gel column (Baker). After cooling, elution with chloroform gave 20.6 g (40%), mp 211–215.5°, of essentially pure material. Two recrystallizations from methanol yielded 13.2 g (25.6%) of analytically pure 4-bromoestradiol (II): mp 213.5–215° (lit.[2] mp 207–208°); $[\alpha]^{25}D$ +43° (1%, chloroform) (lit.[2] +129°).[15] Thin layer chromatography (silica gel–chloroform with 5% acetonitrile) showed a single spot (R_f 0.30), and phase solubility analysis indicated 100% purity. Ultraviolet absorptions were at λ_{max}^{MeOH} 283 mμ (ε 2220) [lit.[2] 283 mμ (ε 2240)] and 288 mμ (ε 2200) (lit.[2] none reported).[15,16] The infrared spectrum (in Nujol) exhibited bands at 3200 and 3540 (HO), and 1600 and 1560 cm^{-1} (Ph). The nmr spectrum (in deuteriopyridine) was consistent with the *ortho* proton structure, with a quartet centered at τ 2.82 (J = 8.8 cps) and a singlet at 9.03 (18-CH_3).

Anal.[17] Calcd for $C_{18}H_{23}O_2Br$ (351.3): C, 61.54; H, 6.60; Br, 22.75. Found: C, 61.40; H, 6.58; Br, 22.46.

Treatment of the 4-bromoestradiol (II) with pyridine and acetic anhydride at 25° gave the 4-bromoestradiol diacetate (IV): mp 175.5–177.5° (lit.[2] mp 143–144°); λ_{max}^{MeOH} 269 and 277 mμ (ε 466 and 440) [lit.[2] 275 mμ (ε 1280)]; $[\alpha]D$ +25° (1%, chloroform) (lit.[2] +103°). A hydrolytic acetyl determination confirmed the presence of two acetate groups.

2-Bromoestradiol (III).—By concentration of the mother liquor from the separation of the 4 isomer to a volume of 250 ml solids weighing 16 g separated overnight. Chromatography of these on 400 g of silica gel (Baker) on elution with chloroform with 2% acetonitrile gave 12 g of solids, which were acetylated overnight at 25° in a mixture of 120 ml of dry pyridine and 120 ml of acetic anhydride. Addition of ice water gave a solid which was recrystallized twice from ethanol to give 7.3 g of 2-bromoestradiol diacetate (V): mp 166–168° (lit.[2] mp 162–163°); $[\alpha]^{25}D$ +41°

(12) Prepared by us according to Woodward.[8]
(13) A. J. Tomson and J. P. Horwitz, *J. Org. Chem.*, **24**, 2056 (1959).
(14) S. Kraychy and T. F. Gallagher, *J. Biol. Chem.*, **229**, 519 (1957).
(15) Further recrystallizations from methanol did not alter the physical data given. As to discrepancies with literature values please see text.
(16) Small amounts of 2- and 4-bromoestradiol prepared *via* a Sandmeyer reaction on the aminoestrone methyl ethers showed ultraviolet data similar to ours.
(17) All analytical samples were dried at 95° (0.1 mm) for 20 hr.

(1%, chloroform) (lit.[2] +109°); λ_{max}^{MeOH} 282.5 and 275 mμ (ε 1490 and 1270) [lit.[2] 269 mμ (ε 530)]. Hydrolysis by stirring the suspended diacetate in 70 ml of methanol with 37 ml of a 10% aqueous potassium hydroxide solution at 25° gave a clear solution overnight, which was acidified (pH = 6) and diluted with 65 ml of water. The methanol was removed under vacuum, the suspension was chilled, and the solids were recrystallized from ethanol to yield 4.5 g of crystals, mp 197–198°, in which a small impurity (2,4-dibromoestradiol, R_f 0.39) was still present. The material was dissolved in 90 ml of ethanol, basified with 0.8 g of potassium hydroxide in 3 ml of water, and diluted with 90 ml of water. Fractional precipitation by the cautious addition of 12.5 ml of 1 *N* hydrochloric acid in five equal increments with vigorous stirring gave five crops of material. Three of these, samples 2, 3, and 4, were recrystallized from ethanol to give 2.8 g (5.5%) of analytically pure 2-bromoestradiol (III): mp 197–198° (lit.[2] 156–157°); $[\alpha]^{25}D$ +104° (1%, chloroform) (lit.[2] +132°).[15] Thin layer chromatography (silica gel–chloroform with 5% acetonitrile) showed a single spot (R_f 0.34); vapor phase chromatography exhibited a single peak. Ultraviolet absorptions were at λ_{max}^{MeOH} 287 mμ (ε 3440), shoulder at 292 mμ (ε 3230) [lit.[2] 281 mμ (ε 2320)].[15,16] The infrared spectrum (in Nujol) exhibited bands at 3620, 3590, and 3260 (OH) and 1600, 1560, and 1480 cm^{-1} (Ph). The nmr spectrum (in deuteriopyridine) was consistent with the assigned structure, showing no discernible splitting of the *para* protons and a pair of singlets at τ 2.39 and 2.97 and a singlet at 9.13 (18-CH_3).

Anal. Found: C, 61.30; H, 6.71; Br, 22.85 (for calculated values, see above).

Registry No.—II, 1630-83-7; III, 15833-07-5; IV, 15833-06-4; V, 15856-39-0.

Acknowledgments.—The authors wish to thank Dr. Byron H. Arison for interpretation of the nmr spectra, Mr. Richard N. Boos and his staff for the elemental analyses, Mr. Alec Kalowsky for the ultraviolet spectra, and Mr. Frederick Lostbourne for the optical rotation measurements.

Total Synthesis of *dl*-Sabinene, *dl-trans*-Sabinene Hydrate, and Related Monoterpenes

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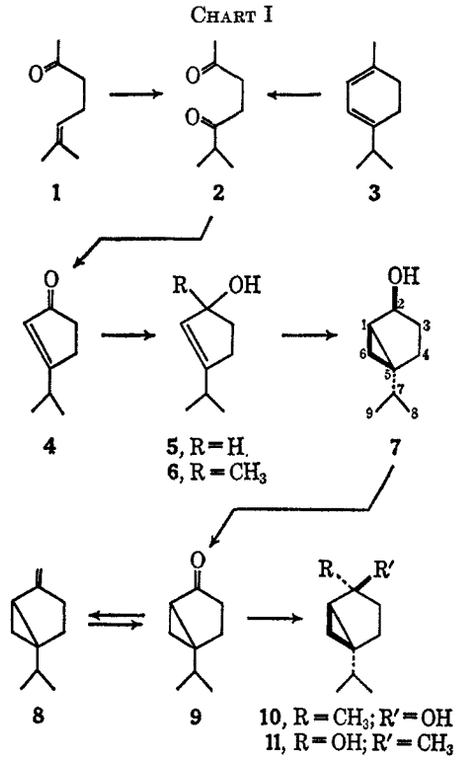
Despite the frequent occurrence of monoterpenes possessing the bicyclo[3.1.0]hexane ring system in essential oils, synthetic approaches to these substances have received little attention. As part of an over-all program directed toward the synthesis of mono- and sesquiterpenes, we investigated the construction of several representative bicyclo[3.1.0]hexanes of the sabinane group: sabinene (**8**),[1,2] sabina ketone (**9**),[3] and *cis*- and *trans*-sabinene hydrates (**10** and **11**).[4,5] Sabinene is reported to be present in a wide variety of essential oils including savin oil,[6] lavandin oil,[7] *Juniperus horizontalis* leaf oil,[8] and citrus oils[9] while sabina ketone is reportedly present in lavandin oil.[10] Although *cis*-sabinene hydrate has not been found in nature, the *trans* isomer represents a small but very important part of a number of mint oils.[5,11–13]

Although Eastman and coworkers[5] have reported the preparation of *cis*- and *trans*-sabinene hydrates from naturally occurring sabinene, no total syntheses of any of these materials has come to our attention.[13a] We wish to report here the total syntheses of racemic counterparts of the aforementioned members (**8**–**11**) of the sabinane group.

Our initial synthetic objective was *cis*-sabinene hydrate (**10**). Several reports, including an extensive investigation by Dauben and Berezin,[14] note that allylic and homoallylic alcohols react with the Simmons–Smith reagent[15] *via* participation of the hydroxyl function. This interaction results in a product having the alcohol function and the newly generated cyclopropyl ring in a *cis* relationship to one another. With this fact in mind, a synthetic scheme which is quite stereoselective can be visualized along lines outlined in Chart I.

CHART I



The required starting dione 2 was available by either of two procedures. The readily available 2-methyl-2-hepten-6-one (**1**) was hydroborated with 2 equiv of

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(2) E. Guenther, "The Essential Oils," Vol. II, D. Van Nostrand Co., New York, N. Y., 1949, pp 64–65, and references therein.

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(6) A. B. Booth, *Amer. Perfumer Aromat.*, **69**, 45 (1957); *Chem. Abstr.*, **51**, 7658 (1957).

(7) I. Calvarno, *Essenze Deriv. Agrumari*, **34**, 169 (1964); *Chem. Abstr.*, **63**, 5443 (1965).

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(9) R. M. Ikeda, W. L. Stanley, L. A. Rolle, and S. H. Vannier, *J. Food Sci.*, **27**, 593 (1962); *Chem. Abstr.*, **60**, 7371 (1964).

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(12) E. von Rudloff and F. W. Hefendehl, *Can. J. Chem.*, **44**, 2015 (1966).

(13) I. C. Nigam and L. Levi, *J. Agr. Food Chem.*, **11**, 276 (1963).

(13a) NOTE ADDED IN PROOF.—Since submission of this manuscript, a total synthesis of sabina ketone and sabinene by a different route has been reported: M. Marx, Ph.D. Thesis, Columbia University, New York, N. Y., 1966; *Dissertation Abstr.*, **27**, 4266-B (1967).

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(15) H. E. Simmons and R. D. Smith, *ibid.*, **81**, 4256 (1959).