Rearrangement Reactions of 4-Bromoisophorone[1]

JOHN N. MARX,* ARTHUR W. CARNRICK,[2] AND JAMES H. COX[2]

Department of Chemistry, Texas Tech University, Lubbock, Texas 79409

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4-Bromoisophorone (Ib) is shown to undergo two types of rearrangment reactions with nucleophiles: eliminative aromatization to 3,4,5-trimethylphenol (XI) and 2,3,5-trimethylphenol (XII), and S_N2' attack, followed by double bond migration, to give 2-substituted isophorone derivatives III. The report of direct S_N2 substitution to yield 4-substituted isophorone derivatives is shown to be in error. Thus, reaction of Ib with NaOH gives the two phenols XI and XII, as well as 2-hydroxyisophorone (IIIc) and the six dimers IV–IX, derived from O- and C-alkylation of the phenols XI and XII by 4-bromoisophorone. The reaction with silver acetate gives the phenols XI and XII, the dimer X, derived from oxidative coupling of XI, and the allylic acetate IId. Reaction with sodium iodide gives the allylic iodide IIe, which gives mainly XI but no XII when treated with NaOH or AgOAc.

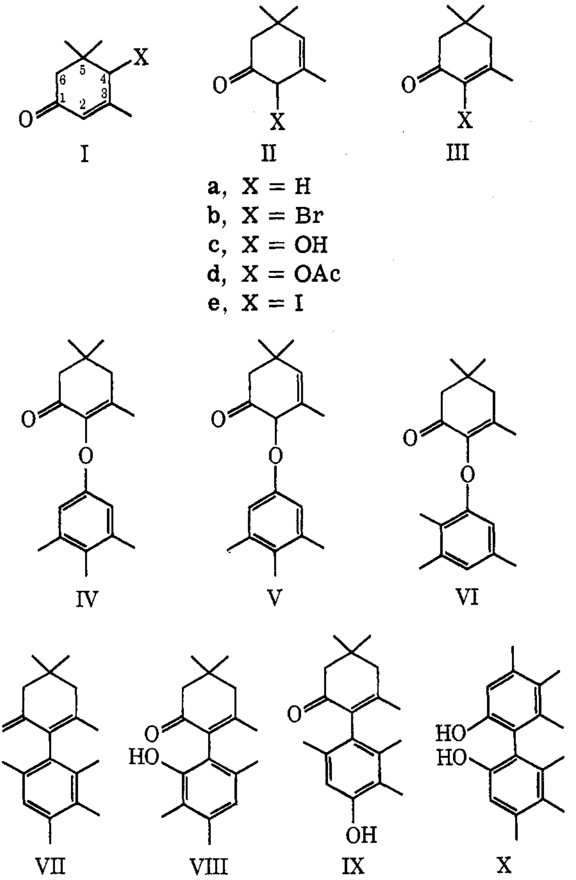
In 1957, Edgar, Harper, and Kazi[3] reported the synthesis of 4-bromoisophorone (Ib) and some substitution reactions it undergoes, including its hydrolysis in base to 4-hydroxyisophorone (Ic). In connection with terpene syntheses, we desired a less temperamental route to 4-hydroxyisophorone than that afforded by the usual route through deconjugation of isophorone (Ia) to β-phorone (IIa).[4,5] We have therefore tried to repeat the work of Edgar, Harper, and Kazi and find that in our hands only rearrangement products are formed from 4-bromoisophorone in base-catalyzed hydrolysis or reaction with silver acetate.

Most allylic oxidants react with isophorone at the C-6 and/or the C-7 positions,[6] rather than at C-4, presumably for steric reasons. However, the reaction of isophorone with *N*-bromosuccinimide gives 4-bromoisophorone in about 50% yield, as reported.[3] The nmr, uv, and ir spectra are in accord with this formulation. Although the nmr spectrum for 6-bromoisophorone would also be expected to be very similar to that observed, the allylic coupling (J = 1 Hz) observed between the C-2 and C-4 proton signals verifies that the compound actually is 4-bromoisophorone.[7]

The reaction of 4-bromoisophorone with aqueous $NaHCO_3$ is reported[3] to lead to a compound assumed to be 4-hydroxyisophorone (Ic) (not obtained pure)[9] and 3,4,5-trimethylphenol, in about equal amounts, as the only distillable materials. In our hands, a number of products were obtained, including 3,4,5-trimethylphenol and much starting material, but no 4-hydroxyisophorone (Ic) could be detected. In particular, the nmr spectrum of the total reaction mixture showed no peaks in the τ 4–6 region except those of the starting material, thus revealing the absence of the C-2 and C-4 protons of 4-hydroxyisophorone.[4c]

More vigorous reaction conditions or the use of NaOH instead of $NaHCO_3$ gave rise to complete reaction of the 4-bromoisophorone. Under the latter conditions, nine products were isolated and identified. The base-soluble compounds were identified as 3,4,5-trimethylphenol (12%), 2,3,5-trimethylphenol (4%), and the diosphenol, 2-hydroxyisophorone (IIIc) (5%), by comparison with authentic samples. The neutral fraction of the reaction mixture contained six new dimeric compounds, which were separated by column chromatography and crystallization. They are all products derived from attack of the anions of the two initially formed phenols on 4-bromoisophorone, and are assigned structures IV through IX (Chart I) on the basis of their

CHART I



a, X = H
b, X = Br
c, X = OH
d, X = OAc
e, X = I

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[1] Reported at Southeast–Southwest Regional Meeting of the American Chemical Society, New Orleans, La., Dec 3, 1970, Abstract #440.

[2] Robert A. Welch Undergraduate Research Scholars.

[3] A. J. B. Edgar, S. H. Harper, and M. A. Kazi, *J. Chem. Soc.*, 1083 (1957).

[4] (a) M. S. Kharasch and P. O. Tawney, *J. Amer. Chem. Soc.*, **63**, 2308 (1941); (b) O. Isler, H. Lindlar, M. Montavon, R. Ruegg, G. Saucy, and P. Zeller, *Helv. Chim. Acta*, **39**, 2041 (1956); (c) J. N. Marx and F. Sondheimer, *Tetrahedron, Suppl. VIII*, Part I, 1 (1966).

[5] Since this work was carried out, an improved procedure for the synthesis of β-phorone has been reported: J. Meinwald and L. Hendry, *J. Org. Chem.*, **36**, 1446 (1971).

[6] (a) J. W. Ellis, *ibid.*, **34**, 1154 (1969); (b) E. M. Kosower and G.-S. Wu, *ibid.*, **28**, 633 (1963); (c) W. von E. Doering and F. J. Beringer, *J. Amer. Chem. Soc.*, **71**, 2221 (1949).

[7] The reaction of isophorone with bromine in CCl_4, on the other hand, gives a very complex mixture of bromination products, and the HBr salt of isophorone crystallizes from the mixture.[8] However, the use of solid $NaHCO_3$ in large excess to remove the HBr as it is formed gives rise to 4-bromoisophorone (Ib) as the major product. The yield is almost quantitative on a small scale, at −10°, but decreases dramatically on scaling up the reaction, so that the use of NBS is the preferred route.

[8] J. N. Marx, *Tetrahedron Lett.*, **No. 40**, 3517 (1970).

[9] The uv and ir spectra reported for the impure compound assumed to be 4-hydroxyisophorone (Ic) could also be accommodated by the diosphenol IIIc.

nmr spectra (see Experimental Section) and their independent syntheses.

The major neutral product (50%) was identified as the dimeric ether IV. Its nmr spectrum showed two equivalent methyl groups and two equivalent protons attached to an aromatic ring as well as one other aromatic methyl group and protons characteristic of a 2-substituted isophorone derivative. Compound IV was synthesized independently in high yield from the reaction of sodium 3,4,5-trimethylphenoxide with 4-bromoisophorone, thus completing its structure proof. The only other product formed in this reaction was a phenolic ketone, whose spectral data and method of synthesis identified it as VII. Compound VII was also identified as a minor product from the original reaction of 4-bromoisophorone with NaOH.

Some chromatographic fractions containing the dimeric ether IV were contaminated with a very similar compound, which showed all the same nmr peaks, but the singlet in the aromatic region at τ 3.49 integrated for about three protons instead of two. This signal could be resolved into two signals at τ 3.45 and 3.57 by use of benzene as the nmr solvent. Pure IV showed only the τ 3.45 peak under these conditions. The uv spectrum showed the 242-nm peak due to IV, as well as end absorption and weak absorption at 280 (aromatic ring) and 300 nm (carbonyl). The contaminant was assigned the nonconjugated structure V, which is the assumed precursor of IV. Attempts at further purification of the mixture failed, but treatment with NaOH converted it completely into the conjugated compound IV, thus verifying the structural assignment. Several attempts to synthesize pure V from sodium 3,4,5-trimethylphenoxide and 4-bromoisophorone under mild conditions gave only IV.

Another dimer isolated from the original reaction mixture was the ether VI derived from attack of 2,3,5-trimethylphenoxide on 4-bromoisophorone. Its nmr spectrum showed three nonequivalent methyls and two nonequivalent hydrogens on the aromatic ring. It could be synthesized in high yield from the reaction of sodium 2,3,5-trimethylphenoxide with 4-bromoisophorone. This reaction also gave two minor phenolic ketone dimers, identified as VIII and IX, which were also isolated from the original reaction mixture. Although the nmr spectra did not allow unambiguous structural assignments, VIII is identified as the ortho-substituted phenol, since it formed a stable crystalline chelate with $FeCl_3$ (as did VII) but the para isomer IX gave only a green color.

Thus, 4-bromoisophorone (Ib) undergoes two fundamental types of reactions in aqueous base, aromatization and substitution with allylic rearrangement (S_N2′). The compound can be considered as a neopentyl allylic bromide, for which direct elimination reactions are impossible. The present work demonstrates that direct S_N2 reactions do not occur, presumably because the 4 position is very sterically blocked. However, the 2 position is more sterically accessible, and nucleophilic attack there occurs readily. Attack of hydroxide ion leads to the diosphenol IIIc, but aromatization competes. As the anions derived from XI and XII build up, they attack the 4-bromoisophorone in the S_N2' manner, both through oxygen and carbon, giving rise to the dimers IV–IX. This reaction is very efficient, in accord with the greater nucleophilicity expected for phenoxides over hydroxide, as shown by the fact that no aromatization occurred when the preformed phenoxides were allowed to react with 4-bromoisophorone.[10] In these reactions, the deconjugated isomers doubtlessly are formed first and are isomerized by the base to the more stable conjugated isomers, but except for V they could not be detected.

Edgar, Harper, and Kazi[3] report that the reaction of AgOAc with 4-bromoisophorone occurs without rearrangement to give 4-acetoxyisophorone (Id). However, we can detect no product which has the expected nmr spectrum. Four products have been isolated from this reaction, in yields quite dependent on the exact reaction conditions. These are 3,4,5-trimethylphenol (XI) (60–80%), 2,3,5-trimethylphenol (XII) (5–15%), the allylic acetate IId (5–10%), and the phenolic dimer X (5–15%). In addition, a complex mixture of unidentified compounds was formed if the reaction was not protected from the air.

The uv and ir spectra of the allylic acetate IId were characteristic of a nonconjugated cyclohexenone. Its nmr spectrum showed one vinyl proton signal at τ 4.18 and one proton signal at τ 4.54. This latter is consistent with the C-2 proton in IId, deshielded by three electronegative groups. For comparison, the C-4 proton signal of Ib appears at τ 5.67.

The phenolic dimer X could be synthesized independently by oxidative coupling of 3,4,5-trimethylphenol with AgOAc, and doubtlessly arises from this source in the original reaction. This suggestion is strengthened by the fact that metallic silver is also formed in the reaction.

Thus, the reaction with AgOAc gives mainly aromatization, but the allylic acetate IId is formed as a product of S_N2' attack. Under the more neutral conditions of the AgOAc reaction, the double bond does not migrate into conjugation, as in the NaOH reaction above. However, the double bond probably does migrate thermally, since IId has an identical retention time with that of authentic IIId, prepared by acetylation[11] of diosphenol IIIc, on three different gas chromatographic columns.[12]

The aromatization reaction requires comment, especially to explain the formation of 2,3,5-trimethylphenol (XII). The reaction must involve carbonium ion formation, followed by a 1,2 shift of a methyl group,[13] and proton loss (Chart II), since the ratio of 3,4,5-trimethylphenol and its further transformation products to 2,3,5-trimethylphenol and its products is *ca.* 10:1 from either the reaction of NaOH or AgOAc on 4-bromoisophorone (Ia). The allylic carbonium ion A formed initially, however, should be destabilized

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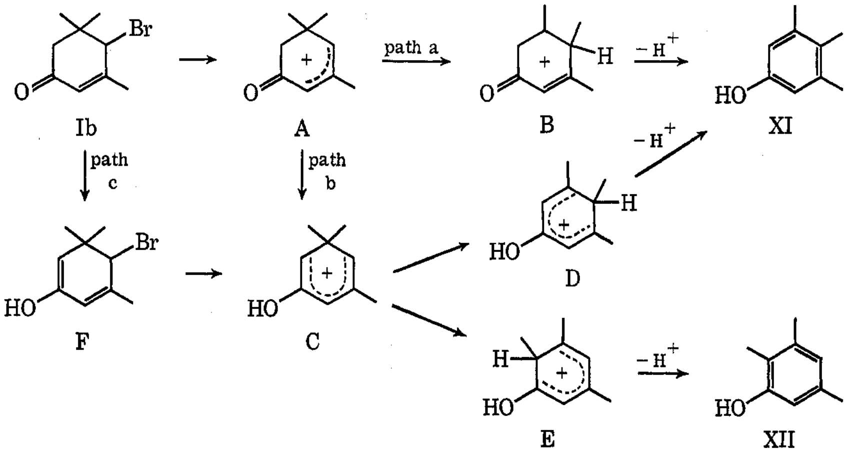
[10] Besides the reactions mentioned in the structure proof, the reaction of 4-bromoisophorone with *p*-cresol in base gave only the ether and phenolic ketone analogous to IV and VI derived from the *p*-cresol.

[11] C. Maignan, J. C. Grandguillot, and F. Rouessac, *Bull. Soc. Chim. Fr.*, 2019 (1970).

[12] The "4-acetoxyisophorone" obtained by Edgar, Harper, and Kazi[3] by distillation of the reaction mixture is probably IIId, although we did not obtain enough of the product to distil it and prove the point, since a large-scale run gave almost only phenolic material. Doubtlessly, the chrysanthemate esters these authors report have rearranged structures also, but this was not investigated.

[13] A referee has suggested that the formation of 2,3,5-trimethylphenol could also be rationalized by a 1,4-methyl migration in ion A. This is ruled out by the fact that the iodo compound IIe gives no 2,3,5-trimethylphenol, yet must rearrange through the ion A.

CHART II



by the adjacent carbonyl group.[14] To avoid this difficulty, the methyl migration could be rather concerted with ionization of the bromide (path a), such that a large amount of positive charge density will not accumulate during the rearrangement step. Alternatively, the ion A can enolize to give the ion C, in which migration can occur to either side, or else ion C could be derived from the enol F (path c). The ion C would be expected to have greater positive charge density at the 4 position than at the 6 position (equivalent to the 2 position in the phenols), and so the *ca.* 10:1 ratio of the phenols XI and XII might be explained without invoking ion A. The enol F would be expected to ionize readily, and thus we favor path c instead of a competition between paths a and b to explain the results. In the NaOH reaction, the zwitterion derived from ion C by proton abstraction may be the actual intermediate, but the arguments are similar.

With the failure to obtain products of direct substitution of 4-bromoisophorone, we attempted to synthesize 4-iodoisophorone (Ie), in order to investigate the effect of a better leaving group on the substitution reactions. However, treatment of Ib with excess NaI in DMSO gave only the allylically rearranged iodide IIe. This compound decomposes slowly on storage, and reacts very rapidly with nucleophiles. For example, the reaction with NaOH gives almost exclusively 3,4,5-trimethylphenol (XI) and diosphenol (IIIc). Interestingly, no 2,3,5-trimethylphenol could be detected. This suggests that the enolic carbonium ion C (Chart II) is not formed in this case, probably because the iodide is a better leaving group and is in a more sterically open environment; so the postulated concerted methyl migration in ion A would be much more favored in this case.[13]

Treatment of the iodo compound IIe with AgOAc gave almost only 3,4,5-trimethylphenol but no 2,3,5-trimethylphenol. The minor products were the allylic acetate IId, an unidentified compound detectable by vpc, and some isophorone (Ia). The latter probably arose from some decomposition of the starting material, since free iodine is slowly liberated during its formation and handling.

Experimental Section

Bromination of Isophorone (Ia).—To a rapidly stirred mixture of 0.20 g (1.45 mmol) of isophorone in 10 ml of CCl_4 and 1 g of solid $NaHCO_3$ in an ice-salt bath was added 0.23 g (1.45 mmol) of bromine in 5 ml of CCl_4 dropwise over the period of 1 hr. After another 2 hr decolorization was complete. The solid was removed by filtration. The nmr spectrum ($CDCl_3$) showed only the characteristic peaks of 4-bromoisophorone: τ 8.84, 8.73 (3 H each, s, C-5 Me's), 7.87 (3 H, d, $J = 1$ Hz, C-3 Me), 7.88, 7.37 (1 H each, AB quartet, $J = 16$ Hz, C-6 H's), 5.67 (1 H, d, $J = 1$ Hz, C-4 H), 4.13 (1 H, p, $J = 1$ Hz, C-2 H). Removal of the CCl_4 below 40°, the last traces at 0.1 mm, and crystallization from minimum ether gave 0.27 g in two crops of 4-bromoisophorone (85%), mp 55–57° (lit.[3] mp 48–49°), identical with a sample prepared according to ref 3.

In a 20-g scale run (6 hr required for decolorization of Br_2), the nmr spectrum showed a complex mixture of products. By integration of the τ 5.67 peak, it was estimated that 35–40% of the material was 4-bromoisophorone.

Reaction of 4-Bromoisophorone with NaOH.—To a stirred solution of 7.34 g (184 mmol) of NaOH in 150 ml of H_2O was added 20.0 g (92.4 mmol) of 4-bromoisophorone. The mixture was stirred for 48 hr at 25° and was almost neutral, then was separated into a base-soluble fraction (2.8 g) and an ether-soluble fraction (10.3 g).

The base-soluble fraction contained three compounds, as detected by vpc (6 ft × 0.125 in. Apiezon L on Chromosorb G at 200°), identified in order of increasing retention times as the diosphenol IIIc (25%), 2,3,5-trimethylphenol (18%), and 3,4,5-trimethylphenol (57%). The compounds were separated by column chromatography over silica gel (standard chromatographic conditions, a 25 × 1.5 cm column of silica gel was packed in 5% ether–95% petroleum ether (bp 30–60°) by volume; the column was eluted with increasing amounts of ether, given as percentages). Elution with 20% ether gave a mixture of diosphenol III, contaminated with some 2,3,5-trimethylphenol. Sublimination at 0.1 mm gave a pure sample of the diosphenol III, mp 91–93°, identical with an authentic sample, prepared by permanganate oxidation of isophorone[15] or HCl rearrangement of isophorone oxide.[16] Fractions from the column eluted with 25% ether were rich in 2,3,5-trimethylphenol. Crystallization from water gave a pure sample, mp and mmp 93–95°. Fractions eluted with 40% ether gave almost pure 3,4,5-trimethylphenol, crystallized from water, mp and mmp 106–107°.

Direct crystallization from ethanol of the neutral fraction of the original reaction mixture gave 3.5 g (three crops, after recrystallization) of IV: mp 110–111°; uv λ_{max}^{EtOH} 228, 243, 281 nm (shoulder); ir ν_{KBr} 1695, 1640, 1620, 1575 cm^{-1}; nmr ($CDCl_3$) singlets at τ 8.88 (6 H, C-5 Me's), 8.13 (3 H, C-3 Me), 7.94 (3 H, C-4′ Me), 7.79 (6 H, C-3′ and C-5′ Me's), 7.60 (4 H, C-4 and C-6 H's), 3.49 (2 H, aromatic H's).

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[14] L. Pauling, "Nature of the Chemical Bond," Cornell University Press, Ithaca, N. Y., 1948, p 199.

[15] O. Wallach, *Justus Liebigs Ann. Chem.*, **414**, 329 (1916).

[16] G. B. Payne, *J. Org. Chem.*, **24**, 719 (1959).

Anal. Calcd for $C_{18}H_{24}O_2$: C, 79.37; H, 8.88. Found: C, 79.25; H, 8.99.

The mother liquor material was chromatographed on silica gel, using the standard technique described above, using a 3 × 75 cm column. Fractions (50 ml) were collected and recombined on the basis of tlc and nmr analysis. Fractions 1–4 (5% ether in petroleum ether) were empty. Fractions 5–7 (10%) (0.2 g) gave no characterizable material. Fractions 8–9 (10%) (0.1 g) were rechromatographed on silica gel. Crystals of VI (35 mg) were obtained in the 10% fractions: mp 138–140° (EtOH); uv $\lambda_{\max}^{\mathrm{EtOH}}$ 228, 243, 281 nm; ir $\nu_{\mathrm{CCl_4}}$ 1695, 1645, 1620, 1580 cm^{-1}; nmr (CCl_4) all singlets at τ 8.85 (6 H, C-5 Me's), 8.13 (3 H, C-3 Me), 7.82, 7.82, 7.77 (3 H each, aromatic Me's), 7.72 and 7.63 (2 H each, C-4 and C-6 H's), 4.02 and 3.48 (1 H each, aromatic H's).

Anal. Calcd for $C_{18}H_{24}O_2$: C, 79.37; H, 8.88. Found: C, 79.13; H, 8.79.

Chromatography fractions 10–16 (15 and 20%) (2.3 g) gave 0.72 g of IV, mp 110–111°, by crystallization from ethanol. Rechromatography of the mother liquor material on silica gel gave further amounts of IV. The 15% fractions, however, contained mixtures of IV and a very similar compound. Very careful rechromatography of these combined fractions gave, in the 10% fractions after extensive elution, material of mp 95–115°, which was a *ca.* 1:1 mixture of IV and the nonconjugated isomer V. The nmr spectrum of the mixture was almost superimposable on that of compound IV. However, the τ 3.49 signal integrated for about three protons instead of two. Addition of 10% benzene resolved this signal into two peaks at τ 3.45 (due to IV) and 3.57. The uv spectrum shows stronger end absorption, enhanced absorption at $\lambda_{\max}$ 280, and a new low-intensity absorption at 300 nm. Treatment of a portion of the mixture with 5% NaOH for 2 hr at 25° with stirring, followed by acidification and ether extraction, gave only IV, mp 110–111°. Lack of material precluded further characterization or purification of V.

Fractions 17–27 from the original chromatogram (20–35%) (0.3 g) were rechromatographed on silica gel. Only IV, followed by 3,4,5-trimethylphenol and 2,3,5-trimethylphenol, were detected.

Fractions 28–29 (40%) (0.5 g) were rechromatographed on silica gel. The 20% fractions contained VIII (150 mg), difficultly crystallizable from petroleum ether: mp 156–157°; uv $\lambda_{\max}^{\mathrm{EtOH}}$ 221, 245, 288 nm; ir ν_{KBr} 3380, 1650, 1620, 1600, 1570 cm^{-1}; nmr ($CDCl_3$), s at τ 8.87 (6 H, C-5 Me's), 8.27 (3 H, C-3 Me), 8.02, 7.89, 7.77 (3 H each, aromatic Me's), 7.58 (4 H, C-4 and C-6 H's), 3.30 (1 H, aromatic H).

Anal. Calcd for $C_{18}H_{24}O_2$: C, 79.37; H, 8.88. Found: C, 79.46; H, 8.64.

To a chloroform solution of VIII was added $FeCl_3$ in chloroform. Addition of a few drops of pyridine gave an orange-brown iron chelate containing pyridine: mp 107–110°; ir ν_{KBr} 2375, 1610, 1530, 745, and 675 cm^{-1}. No signals were detectable by nmr.

Original chromatogram fractions 30–39 (40–65%) (2.1 g) were rechromatographed on silica gel. Fractions eluted with 20–30% gave 40 mg of VII, difficultly crystallizable from petroleum ether: mp 161–165°; uv $\lambda_{\max}^{\mathrm{EtOH}}$ 221, 245, 288 nm; ir ν_{KBr} 3330, 1660, 1630, and 1580 cm^{-1}; nmr ($CDCl_3$), all singlets at τ 8.84 (6 H, C-5 Me's), 8.38 (3 H, C-3 Me), 8.09, 8.09, 7.95 (3 H each, aromatic Me's), 7.56 (4 H, C-4 and C-6 H's), 3.70 (1 H, aromatic H).

Anal. Calcd for $C_{18}H_{24}O_2$: C, 79.37; H, 8.88. Found: C, 78.94; H, 8.80.

The compound formed an orange-brown ferric chelate in the presence of pyridine, mp 155–157°. Not enough material was available for further characterization.

Further elution of the column from the rechromatography of original fractions 30–39 gave, in the 30–40% fractions, 25 mg of compound IX, difficultly crystallizable from petroleum ether: mp 142–145°; uv $\lambda_{\max}^{\mathrm{EtOH}}$ 222, 244, 291 nm; ir ν_{KBr} 3330, 1650, 1635 (sh), 1620 (sh), 1560 cm^{-1}; nmr ($CDCl_3$) all singlets at τ 8.87 (6 H, C-5 Me's), 8.29 (3 H, C-3 Me), 8.04, 7.91, 7.79 (3 H each, aromatic Me's), 7.58 (4 H, C-4 and C-6 H's), 3.41 (1 H, aromatic H).

This compound gave a green color with $FeCl_3$ and pyridine in $CHCl_3$, but no chelate could be obtained.

Reaction of 4-Bromoisophorone with Silver Acetate.—A stirred mixture of 20.01 g of 4-bromoisophorone and 15.75 g of silver acetate in 150 ml of glacial acetic acid was heated at 90° for 3 hr as reported.[3] A finely divided precipitate of metallic silver and AgBr formed. The mixture was filtered, diluted with water, extracted with ether, washed with $NaHCO_3$ and then water, and dried over $MgSO_4$, and the solvent was removed to give 19.51 g of material showing much starting material (strong Beilstein test) and several new peaks by nmr analysis. The material was dissolved in 150 ml of acetic acid, another 10.00 g of AgOAc was added, and the mixture was heated at 80° for 17 hr. After work-up as before, 11.20 g of material was obtained. The viscous oil deposited, in three crops, 0.40 g of the phenol dimer X: mp 240–241° (acetone); uv $\lambda_{\max}^{\mathrm{EtOH}}$ 286 nm (ϵ 10,600); $\lambda_{\max}^{\mathrm{EtOH+NaOH}}$ 304 nm; ir $\nu_{\max}^{\mathrm{KBr}}$ 3500, 1610, 1570, 860 cm^{-1}; nmr ($CDCl_3$) τ 8.07, 7.78, 7.71 (3 H each, s), 3.27 (1 H, s).

Anal. Calcd for $C_{18}H_{22}O_2$: C, 79.96; H, 8.20. Found: C, 79.82; H, 8.13.

A solution of X in concentrated H_2SO_4 showed nmr peaks at *ca.* τ 7.3, 7.7, and 8.0 (3 H each, s). This is consistent with sulfonation of X ortho to the phenol. No attempt was made to isolate the sulfonated product.

On treatment of X with acetic anhydride in pyridine overnight at room temperature, the corresponding diacetate was obtained: mp 132.9–133.5° (from ether); nmr ($CDCl_3$) τ 8.13 (3 H, s, OAc), 8.08, 7.80, 7.67 (3 H each, s, Me's), 3.18 (1 H, s).

To a solution of 1.006 g of 3,4,5-trimethylphenol was added 1.229 g of AgOAc in 10 ml of HOAc. The mixture was stirred and heated at 80° for 15 hr. Silver metal was filtered off, and the products were recovered by ether extraction. Crystallization from 5 ml of ether gave 0.102 g (10.2%) of X, mp 238–240°. The material remaining in the mother liquors was almost pure 3,4,5-trimethylphenol, as judged by the nmr spectrum.

The material remaining in the mother liquors from the original reaction of 4-bromoisophorone with AgOAc, after removal of X, was extracted well with 10% NaOH. The material recovered after acidification of the base layer was identified by vpc and nmr analysis as a 80:20 mixture of 3,4,5-trimethylphenol (XI) and 2,3,5-trimethylphenol.

The neutral material from the above extraction (5.8 g) was absorbed on 50 g of silica gel and placed on top of a column of 350 g of silica gel packed with 10% ether–90% petroleum ether (bp 40–60°). Fractions of 50 ml were collected, and the progress of the chromatogram was monitored by nmr analysis. Most fractions contained complex mixtures of products which could not be identified or purified further. However, fractions eluted with 25% ether–75% petroleum ether gave 0.696 g of material which was mainly the allylic acetate IId. Rechromatography gave a pure sample: uv, end absorption; ir $\nu_{\max}^{\mathrm{CCl_4}}$ 1710, 1725, 1670 cm^{-1}; nmr τ 9.02 and 8.99 (3 H each, s, C-5 Me's), 8.14 (3 H, d, J = 1 Hz, C-3 Me), 7.89 (3 H, s, OAc), 7.75 (2 H, s, C-6 H's), 4.54 (1 H, d, J = 1 Hz, C-2 H), 4.18 (1 H, p, J = 1 Hz, C-4 H). This compound had an identical retention time with that of a sample of IIId,[9] prepared by treatment of the diosphenol IIIc[8] with Ac_2O (reflux overnight, followed by evaporation of the Ac_2O; this compound hydrolyzes rather easily) on SE-30, DEGS, and Apiezon L vpc columns at 120–200°, suggesting that isomerization was occurring at these temperatures.

In another run, 20.00 g of AgOAc and 20.00 g of 4-bromoisophorone were refluxed for 17 hr in 150 ml of glacial acetic acid under N_2 with protection from light. Silver metal was still formed, but the total reaction mixture was much less complex. Direct crystallization from the recovered oily product mixture gave 1.42 g (12.2%) of the dimer X. Nmr analysis of the remaining material showed mostly 3,4,5-trimethylphenol, which could be obtained by direct crystallization from ethanol. Gas chromatography showed only 3,4,5-trimethylphenol (76%), 2,3,5-trimethylphenol (19%), and the allylic acetate (5%).

Reaction of 4-Bromoisophorone with NaI. Allylic Iodide IIe.[17]—To a solution of 5.00 g (23.5 mmol) of 4-bromoisophorone (Ib) in 50 ml of dimethyl sulfoxide was added 5.00 g (34.75 mmol) of NaI at room temperature with protection from light. After 10 min of stirring, solution was complete. After 24 hr, water was added, the mixture was extracted well with ether, washed with $NaHSO_3$ to remove I_2, washed with water, and dried over $MgSO_4$, and the ether was removed at the aspirator below 20° to give 5.25 g of product. Nmr analysis showed that the product was *ca.* 65% of unreacted 4-bromoisophorone (Ib) and 35% of the allylic iodide IIe, by the ratio of the peaks at τ 5.67 and 5.53, respectively. The material was resubmitted for a further 24 hr with 5.00 g of NaI in 50 ml of DMSO. Nmr

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(17) We thank Don Guion for developing this reaction.

analysis now revealed that the reaction was 80% complete. After the product was resubmitted to the reaction conditions for a further 24 hr, the starting material Ib was not detectable by nmr. The product (3.02 g), which was very unstable and liberated iodine on standing or heating, had an nmr spectrum as follows: τ 8.77, 8.69 (3 H each, C-5 Me's), 7.77 (3 H, d, $J = 1$ Hz, C-3 Me), 7.75 (2 H, broad s, C-6 H's), 5.53 (1 H, d, $J = 1$ Hz, C-2 H), 4.13 (1 H, p, $J = 1$ Hz, C-4 H). Peaks for small amounts of contaminants could be observed in the upfield region in all preparations of IIe, but the compound could not be purified, so it was used immediately in subsequent reactions. In one run the reaction was allowed to proceed for 2 weeks, but a 40:60 ratio of IIe to Ib remained.

An 0.0413-g sample of IIe, when treated with excess $AgNO_3$, gave 0.0219 g of AgI (calcd 0.0224 g).

Reaction of Iodide IIe with NaOH.—To a stirred solution of 0.32 g of NaOH in 10 ml of H_2O was added 1.0 g of freshly prepared IIe. After 15 min at room temperature, the reaction mixture had become almost neutral. Analysis of the product by vpc and nmr revealed 70% 3,4,5-trimethylphenol (XI) and 25% diosphenol IIIc and small amounts of isophorone and unidentified substances. 2,3,5-Trimethylphenol (XII) was shown to be absent.

Reaction of Iodide IIe with AgOAc.—To a stirred solution of 2.51 g of AgOAc in 20 ml of glacial HOAc was added 2.0 g of freshly prepared IIe. The reaction mixture, protected from light and air, was stirred for 15 min at room temperature, then heated to 80° for 20 min. Filtration and ether extraction gave 0.80 g of material which was separated into base-soluble (0.40 g) and neutral (0.37 g) fractions. Gas chromatographic analysis revealed that the neutral layer contained 45% of the allylic acetate IId, 15% of isophorone, and 40% of an unidentified product. The base-soluble material was 3,4,5-trimethylphenol (70%) and diosphenol IIc (30%).

Registry No.—Ib, 16004-91-4; IId, 34638-12-5; IIe, 34638-13-6; IIIc, 34638-14-7; IV, 34638-15-8; V, 34638-16-9; VI, 34638-17-0; VII, 34638-18-1; VIII, 34638-19-2; IX, 34638-20-5; X, 34638-21-6; X diacetate, 34638-22-7.

Acknowledgment.—We wish to thank the Robert A. Welch Foundation for support of this work.

The Chemistry of the *trans*-Trimethylenenorbornene Ring System. I. A General Synthesis of 9,9-Disubstituted *trans*-5,6-Trimethylene-2-norbornene Derivatives[1a,b]

GEORGE B. CLEMANS,* M. N. ESSIET,[1c] AND R. L. TYSON[1c]

Department of Chemistry, Bowling Green State University, Bowling Green, Ohio 43403

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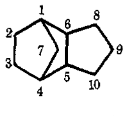
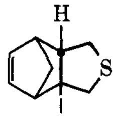
Condensation of *trans*-5,6-dimethylol-2-norbornene ditosylate and diethyl malonate with potassium *tert*-butoxide in *tert*-butyl alcohol afforded a mixture of cyclized products from which 9,9-dicarbo-*tert*-butoxy-*trans*-5,6-trimethylene-2-norbornene was readily separable. Saponification of the remaining ester mixture then gave the corresponding dicarboxylic acid. Attempts to prepare related *trans*-trimethylenenorbornenes by Dieckmann cyclization of *trans*-5,6-dicarbethoxymethyl-2-norbornene or the corresponding dimethyl ester and by Thorpe-Ziegler cyclization of *trans*-5,6-dicyanomethyl-2-norbornene were unsuccessful. Infrared and nmr spectra of the cyclized products were interpreted in terms of a high degree of internal strain associated with the *trans*-trimethylene bridge. It was concluded that unusually large distortions of the norbornyl cage occur in these compounds and that the norbornyl cage shows an unexpectedly high capability of accommodating strain.

The dicyclopentadienes[2,3] are known to exist in two distinct isomeric modifications (**1a** and **1b**) having either the endo,cis or exo,cis ring junction.[4] The possibility that similar derivatives containing a trans ring junction might also be prepared was first considered in 1932 but was rejected at that time on steric grounds.[4] A trans structure was later proposed[5] for a product obtained from the isomerization of tetrahydro-*endo*-dicyclopentadiene, but this was subsequently shown to be incorrect.[6] In 1965, however, Wilder and Feliu-Otero reported[7] the sulfide **2**, an heterocyclic derivative of dicyclopentadiene which incorporates a trans five-membered ring. Bachman[8] had previously suggested the *trans*-trimethylenenorbornane **3** as one of several products obtained from the decomposition of certain



1a, endo, cis
b, exo, cis



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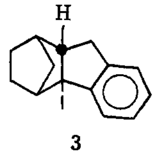

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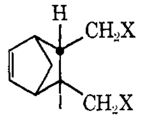

4, X = OTs
5, X = CN
6, X = COOH
7, X = $COOCH_3$
8, X = $COOC_2H_5$

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[1] (a) Grateful acknowledgment is made to the Petroleum Research Fund administered by the American Chemical Society for partial support of this work. (b) Presented in part at the 3rd Central Regional Meeting of the American Chemical Society, Cincinnati, Ohio, June 1971. (c) Taken in part from the M.A. Theses of M. N. E. and R. L. T., Bowling Green State University, Bowling Green, Ohio, 1970–1971.

[2] Of the several systems of nomenclature that have been applied to compounds in this series, the semitrivial *trans*-trimethylenenorbornene system based on that proposed by Schleyer and Donaldson[3] for the corresponding norbornanes will be used throughout the remainder of this report to emphasize the close structural relationship between these compounds and norbornene. The numbering is as in **1**.

[3] P. v. R. Schleyer and M. M. Donaldson, *J. Amer. Chem. Soc.*, **78**, 5702 (1956).

[4] K. Alder and G. Stein, *Justus Liebigs Ann. Chem.*, **496**, 204 (1932).

[5] G. Egloff, G. Hulla, and V. I. Kormarewsky, "Isomerization of Pure Hydrocarbons," Reinhold, New York, N. Y., 1942, p 122, and references cited therein.

[6] P. v. R. Schleyer and M. M. Donaldson, *J. Amer. Chem. Soc.*, **82**, 4645 (1960).

[7] P. Wilder and L. Feliu-Otero, *J. Org. Chem.*, **30**, 2560 (1965).

[8] G. L. Bachman, Ph.D. Dissertation, Washington University, St. Louis, Mo., 1964.