Conversion of Diethylstilbestrol to a Benzofulvene Derivative

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Dimethyl sulfoxide reacts with diethylstilbestrol in the presence of hydrogen chloride to yield a yellow crystalline dimethylsulfonio derivative of benzofulvene. Its structure was established mainly by n.m.r. analysis beside the more usual techniques applied to the compound and its pyrolysis product. Thin layer chromatography was of help in arriving at a notion of the reaction sequence.

In a continuing study[1] of the preparation and properties of steroids and biologically related compounds bearing dimethylsulfonio groups, the action of dimethyl sulfoxide on diethylstilbestrol in acidic media was investigated. The formation of sulfonium salts by reaction of aromatic hydrocarbons with thionyl chloride in the presence of aluminum chloride has been postulated to involve diphenyl sulfoxide as an intermediate.[2] Phenols and thionyl chloride yield tris(hydroxyaryl)-sulfonium salts.[3] In a preliminary report, Lard and Claypole[4a] showed that phenols react with dimethyl sulfoxide and hydrogen chloride to yield sulfonium salts, which they stated were *o*-dimethylsulfonio phenols. We have found that phenol yields some *p*-hydroxyphenyldimethylsulfonium chloride as well, when benzene is used as the solvent.[4b]

When diethylstilbestrol and dimethyl sulfoxide were added in that order to a freshly prepared solution of hydrogen chloride in nitromethane or nitroethane, a golden yellow precipitate slowly separated. When the order of mixing was reversed, or when aged hydrogen chloride–nitromethane solutions were employed, the product was not obtained and no color developed. The product was soluble in methanol and insoluble in ether. and it gave positive sulfur and halogen tests, suggesting that a sulfonium salt was formed. This was supported by elemental analysis. However, the ultraviolet absorption spectrum indicated that the product was not the result of simple substitution, but that diethylstilbestrol suffered oxidative removal of hydrogen followed by cyclization to a more highly condensed system. The dehydro derivative of diethylstilbestrol, dienestrol (I), is reported to form 1-methyl-3-ethyl-2-*p*-hydroxyphenyl-6-indenol (II) in the presence of acids.[5] Both I and II with dimethyl sulfoxide did give the identical yellow product in yields superior to that from diethylstilbestrol.

The product showed a pK_a value of approximately 7, showing the acid strengthening effect of the dimethylsulfonio groups on phenols. Bordwell and Boutan[6] report a pK_a of 7.3 for *p*-hydroxyphenyldimethylsulfonium *p*-bromobenzenesulfonate and a pK_a of 7.67 for the *meta* isomer. When heated, the compound eliminated the units of methyl chloride and gave a yellow product which showed an ionization constant typical of phenols (pK_a approximately 10). Methylation of the pyrolysis product followed by oxidation yielded *p*-anisic acid. Thus, both phenolic hydroxyl groups were preserved in the sulfonium salt. The infrared spectra of both the sulfonium salt and pyrolysis product showed no band in the carbonyl region.

The nuclear magnetic resonance spectrum of the pyrolysis product in deuterated chloroform with tetramethylsilane as the internal standard at 60 Mc. showed the presence of eighteen hydrogen atoms, sixteen of which were assigned as follows: six aromatic hydrogen atoms, nine occurring in three methyl groups, and one attached to a carbon associated in a double bond.[7] The aromatic proton region was dominated by a strong peak, which was attributed to the protons of the freely-rotating *p*-hydroxylphenyl group. The remainder of the aromatic proton region was a typical AB pattern with coupling constants characteristic of *ortho* protons. Structure III for the sulfonium salt is consistent with these findings. The benzofulvene nucleus is the chromophore.

In contrast to related benzofulvene derivatives,[8] III appeared to be stable for several months.

Other evidence that the sulfonium group was attached at the 4-position of the benzofulvene nucleus was that the infrared spectrum of the sulfonium salt in a potassium bromide pellet showed no absorption bands in the 900–860-cm.$^{-1}$ region, where compounds with solo hydrogen exhibit medium bands.[9] Thus, the preferred structure is III rather than the isomer with the dimethylsulfonio group in the 6-position. Strong bands typical of duo aromatic hydrogen were observed at 816 and 843 cm.$^{-1}$.

Compound III was not obtained when acetonitrile was employed as the solvent. To determine whether nitromethane or nitroethane served as oxidizing agents, solutions of diethylstilbestrol in nitroethane containing hydrogen chloride were kept for varying periods of time and examined by thin layer chromatography on Absorbosil-1[10] in methylene chloride and alcohols. Although the separation of diethylstilbestrol from I and II was not entirely satisfactory (compound II in *t*-butyl alcohol migrated somewhat faster), compound II chromatographed in *n*- or *t*-butyl alcohol showed a brilliant blue fluorescence for several minutes when exposed to ultraviolet light (Mineralight R-51), whether

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[1] N. F. Blau and C. G. Stuckwisch, *J. Org. Chem.*, **27**, 370 (1962).

[2] C. Courtet and T. Y. Tung, *Compt. rend.*, **200**, 1541 (1935).

[3] D. Libermann, *ibid.*, **107**, 921 (1935); **198**, 1421 (1934).

[4] (a) E. W. Lard and D. P. Claypole, *Chem. Eng. News*, **38**, No. 47, 46 (1960); (b) The dimethyl sulfoxide–hydrogen chloride complex is presumed to exist as ion pairs in benzene and electrophilic attack may not be as selective as in ionizing media. The protonated dimethyl sulfoxide ion in excess dimethyl sulfoxide may interact with the phenolic oxygen by dipole attraction, or possibly with the formation of an intermediate such as $ArOS(CH_3)_2^+$, leading to a higher degree of *ortho* substitution.

[5] W. Hausmann and A. E. Wilder Smith, *J. Chem. Soc.*, 1030 (1949).

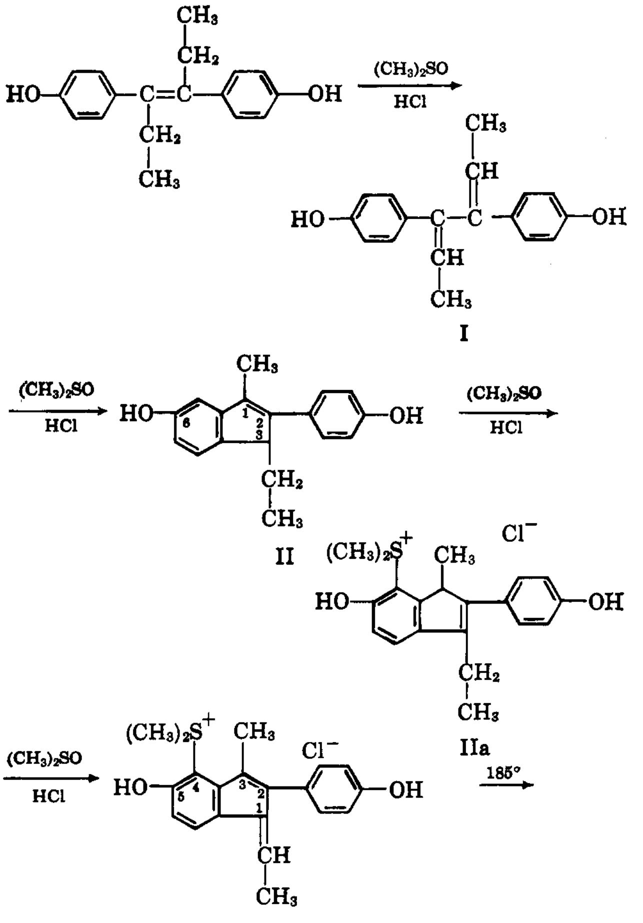
[6] F. B. Bordwell and P. J. Boutan, *J. Am. Chem. Soc.*, **78**, 87 (1956).

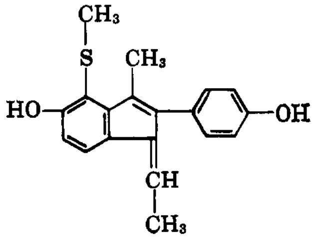
[7] The sulfonium salt was not soluble enough in the usual n.m.r. solvents to give a completely satisfactory spectrum. The spectrum in deuterated dimethyl sulfoxide showed no unexpected gross differences from that of the pyrolysis product.

[8] U. V. Solmssen and E. Wenis, *J. Am. Chem. Soc.*, **70**, 4197 (1948).

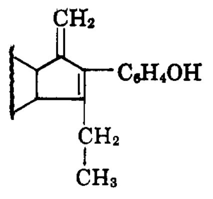
[9] L. J. Bellamy, "The Infrared Spectra of Complex Molecules," 2nd Ed., Metheun and Co., Ltd., London, p. 1958, 79.

[10] Applied Science Laboratories, Inc., State College, Pa.

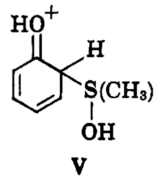




IV



IIIa



V

alone or mixed with diethylstilbestrol. Diethylstilbestrol and compound I treated similarly gave permanent yellow spots. With diethylstilbestrol in nitroethane and hydrogen chloride alone no blue fluorescence was observed. Therefore, compound II was not formed. Neither was diethylstilbestrol oxidized to I, for in that case it would have been converted to II under acid conditions. Chromatograms of samples prepared shortly after dimethyl sulfoxide was added to the mixture showed a blue-green fluorescent spot at the origin, indicating the presence of a highly polar indene derivative which may bear a dimethylsulfonio group, such as IIa. Solutions kept five hours after the addition of dimethyl sulfoxide showed only the yellow spot at the origin typical of III, which does not exhibit the blue fluorescence. Thus, the oxidative removal of the last two hydrogen atoms probably follows the substitution of II. Therefore, it appears that protonated dimethyl sulfoxide and not acidulated nitroethane serves as the oxidizing agent. With a large excess of dimethyl sulfoxide as the solvent, a yellow color does develop but this gives rise to a dark mixture, and from it III was not easily isolated in pure state.

Although the order of the steps leading to III from diethylstilbestrol was not firmly established, the sequence indicated is most probable. Had substitution preceded cyclization, ring closure would be expected to occur on the ring not bearing the deactivating dimethylsulfonio group. The substitution is initiated with electrophilic attack by protonated dimethyl sulfoxide, resulting in the resonance-stabilized ion, indicated by V. The ion suffers elimination of a proton and hydroxide ion to yield the product.

The oxidation of the indene derivative (II) to a substituted benzofulvene could yield two isomeric products. The n.m.r. data, showing a single olefinic proton, clearly indicated that the only isomer isolated is that shown in III, and not that indicated in IIIa.

Some related indene derivatives have been reported to show estrogenic properties; others have been found to be inactive.[8,11] Compound III showed no estrogenic activity, protagonistic or antagonistic, in preliminary tests.

Experimental

Reaction of Diethylstilbestrol with Dimethyl Sulfoxide. 1-Ethylidene-2-*p*-hydroxyphenyl-3-methyl-4-dimethylsulfonio-5-indenol Chloride (III).—A standard solution of hydrogen chloride in ice-cold nitroethane was prepared. Diethylstilbestrol (1.34 g., 0.5 mmole) was dissolved in 50 to 60 ml. of nitroethane, treated with the freshly prepared nitroethane solution containing 1.2 to 1.5 g. of hydrogen chloride, and the volume of the mixture was adjusted to 75 ml. After 15 min., 1.2 ml. (1.3 g., 17 mmoles) of dimethyl sulfoxide was added. The solution became turbid in 3–4 hr. at room temperature and fine, needle-shaped, bright yellow crystals began to separate. These increased in amount during approximately the next 4 hr. The flask or cylinder was usually placed in the ice chest overnight. The crystals were separated, washed with ether, and dried *in vacuo*. The sample weighed from 0.50 to 0.70 g. (27 to 38%) and melted at 180° with decomposition. The melting point varied from 175 to 185°, depending on the rate of heating. A negligible amount of product could be obtained from the mother liquor by precipitation with a large volume of ether. Yields and quality of III varied with the weight of hydrogen chloride in the reaction mixture. The amount given above was optimal. A golden yellow, analytical sample was prepared by precipitation four times from methanol with ether and drying *in vacuo* over calcium chloride or phosphorus pentoxide. The product was hygroscopic and weight increases of 10% in air were observed. Maxima in the ultraviolet absorption spectrum in methanol were observed at 293 (ϵ 30,000) and 338 mμ (9300). The pK_a value for the first dissociation constant estimated potentiometrically in 50% ethanol was 6.9.

Anal. Calcd. for $C_{20}H_{21}Cl\ O_2S$: C, 66.56; H, 5.87; Cl, 9.80; S, 8.89. Found: C, 66.88; H, 5.83; ionic chloride (with silver nitrate in ethanol), 9.61; S, 9.19.

Similar results were observed with nitromethane as the solvent. Diethylstilbestrol is more soluble in nitroethane and it is, therefore, the preferred solvent.

When aged solutions of hydrogen chloride in nitroethane or nitromethane (3–30 days old) were used, a bulky white or grayish precipitate was formed immediately upon addition of dimethyl sulfoxide, and no sulfonium salt was obtained.

Reaction of Dienestrol (I) and 3-Ethyl-1-methyl-2-*p*-hydroxyphenyl-6-indenol (II) with Dimethyl Sulfoxide.—Treatment

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(11) U. V. Solmssen, *Chem. Rev.*, **37**, 481 (1945).

of 1.74 g. (6.5 mmoles) of dienestrol in nitromethane with a solution of 0.50 g. (14 mmoles) of hydrogen chloride in nitromethane and 1.50 g. (19 mmoles) of dimethyl sulfoxide as in the preceding experiment yielded 1.03 g. (45%) of III, melting at 180° with decomposition. Similarly, 0.73 g. (2.7 mmoles) of II, 0.30 g. (8 mmoles) of hydrogen chloride, and 0.47 g. (6.0 mmoles) of dimethyl sulfoxide in nitromethane gave 0.81 g. (83%) of III, melting at 182° with decomposition. Samples of III from the three sources showed identical infrared spectra and gave the same pyrolysis product.

1-Ethylidene-2-*p*-hydroxyphenyl-3-methyl-4-methylthio-5-indenol (IV).—The sulfonium salt III (1.00 g.) was heated under nitrogen at 180–185° for 5 min. The product was cooled, dissolved in benzene, and treated with activated charcoal. The solvents were evaporated, and the residue was crystallized from carbon tetrachloride, yielding 0.75 g. (90%) of yellow product, m.p. 152–153°. The analytical sample, obtained by recrystallization from carbon tetrachloride, melted at 155–156°. The apparent first pK_a, in 50% ethanol, was estimated to be approximately 10. Ultraviolet absorption maxima in methanol at 280 (ϵ 24,000) and 324 mμ (4300) were observed.

Anal. Calcd. for $C_{19}H_{18}O_2S$: C, 73.52; H, 5.84; S, 10.33. Found: C, 73.51; H, 5.68; S, 10.39.

The n.m.r. spectrum of IV showed the presence of eighteen hydrogen atoms with resonances, δ in p.p.m., as follows: 2.0–2.4, nine protons attributed to the three-methyl groups; 5.2, one proton exchangeable with D_2O attributed to one phenolic group; a quartet centered at 6.05, one proton attached to the olefinic carbon of the ethylidene group; 6.7–7.2 (four peaks with the most intense at 6.9), six aromatic protons; a singlet at 7.87, one proton attributed to the 5-hydroxyl group. *o*-Alkylthiophenols are known to form relatively strong hydrogen bonds.[12] A singlet at 7.95 δ was also present in the spectrum of the sulfonium salt.

The pyrolysis product (IV) (0.50 g.), 2.2 ml. of methyl sulfate in 50 ml. of benzene, and a solution of 1.00 g. of sodium hydroxide in 25 ml. of water was shaken for 5 hr. The yellow benzene solution was separated, dried, and evaporated to dryness, yielding 0.27 g. of crude methyl ether, m.p. 100–110°. This was treated with potassium permanganate in acetone at 35° until the violet color persisted. Excess permanganate was decomposed with a drop of alcohol. The mixture was filtered and the filtrate was evaporated to dryness. The residue was dissolved in water and acidified, yielding 0.09 g. of *p*-anisic acid, m.p. and m.m.p. 183–184°, with an authentic sample.

Reaction of Phenol with Dimethyl Sulfoxide in Benzene.—Hydrogen chloride was bubbled for several minutes into a solution of 5.0 g. of phenol and 3.5 g. of dimethyl sulfoxide in 50 ml. of benzene. The mixture was kept overnight at room temperature. The oily layer which had separated was washed with ether and yielded a crystalline product. This was dissolved in methanol and precipitated with ether several times to yield 1.2 g. of *p*-hydroxyphenyldimethylsulfonium chloride, m.p. 160° dec.[13,14] Heating the product several minutes above the melting point gave *p*-hydroxyphenyl methyl sulfide, m.p. 82–83°, in nearly quantitative yield in agreement with the results of Zincke and Ebel.[13]

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[12] E. A. Allan and L. W. Reeves, *J. Phys. Chem.*, **66**, 613 (1962).

[13] T. Zincke and C. Ebel, *Ber.*, **47**, 1100 (1914), report m.p. 159°.

[14] Lard and Claypole (ref. 4) report that the *ortho*-substituted derivative is the product when the reaction is carried out in excess dimethyl sulfoxide. No attempt was made to isolate the *ortho*-substituted derivative in this work.

4-Bromocyclopentene by Hydride Reduction of 3,5-Dibromocyclopentene and Its Unassisted Hydrolysis

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A preparation of 4-bromocyclopentene is described by the reaction of lithium aluminum hydride with the dibromide prepared from cyclopentadiene. This homoallylic bromide undergoes solvolysis in 50% aqueous acetone about four times less rapidly than cyclopentyl bromide. Its unreactivity is discussed in the light of the acceleration by 10^{11} observed in the related but strained 7-norbornenyl sulfonates.

The anchimeric assistance to solvolysis by the double bonds in *anti*-7-norbornenyl[1] and 7-norbornadienyl[2] tosylates (by factors of 10^{11} and 10^{14}, respectively) is the greatest on record; this fact indicates that in the 7-norbornenyl cation the positive charge is effectively delocalized by the overlap of the p-orbitals at C-2, C-3, and C-7, an overlap that is between σ and π in character.

Spectral evidence indicates[3,4] that the same forces which produce a barrier to free rotation in ethane force cyclopentane to adopt a nonplanar conformation. Cyclopentene might exist preferentially, or at least permissibly, in conformation I, and its distortion might become aggravated in 4-bromocyclopentene (II). The obvious resemblance of the conformation II to the C-1-2-3 4-7 portion of 7-norbornenyl bromide led us to prepare the compound and compare its rate of hydrolysis in 50% acetone–water with that of cyclopentyl bromide.

I

II

4-Bromocyclopentene (II), b.p. 43° (35 mm.), $n^{24}\text{D}$ 1.4992, is readily prepared by the S$_N$2′ lithium aluminum hydride reduction of the 1,4-bromination product of cyclopentadiene. The bromide II prepared in this way is free of contamination by its allylic isomer because of the great ease with which the latter is further reduced by lithium aluminum hydride. The bromide II is hydrolyzed in 50% aqueous acetone to the corresponding alcohol (*p*-nitrobenzoate, m.p. 89°). The rate of this hydrolysis, carried out in sealed tubes, was followed by titration with base and compared with that of cyclopentyl bromide, with the results shown in Table I.

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[1] S. Winstein, M. Shatavsky, C. Norton, and R. B. Woodward, *J. Am. Chem. Soc.*, **77**, 4183 (1955); S. Winstein and M. Shatavsky, *ibid.*, **78**, 592 (1956).

[2] S. Winstein and C. Ordronneau, *ibid.*, **82**, 2084 (1960).

[3] J. G. Aston, H. L. Fink, and S. C. Schumann, *ibid.*, **65**, 341 (1943).

[4] K. S. Pitzer, *Science*, **101**, 672 (1945).