TABLE I
FIRST-ORDER RATE CONSTANTS FOR HYDROLYSIS OF THE TETRAMETHYL KETAL OF *p*-BENZOQUINONE IN AQUEOUS SOLUTION AT 25° AS A FUNCTION OF pH[a]

Formation of intermediate		Decomposition of intermediate	
pH	$10^3 k_{obsd}$, sec^{-1}	pH	$10^3 k_{obsd}$, sec^{-1}
5.60	1.83	3.36	0.987
5.56	1.925	3.36	0.917
5.45	2.52	3.02	2.18
5.12	5.13	2.80	3.47
4.94	7.53	2.79	3.27
4.90	6.30	2.61	4.13
4.77	10.66	2.43	6.86
4.56	15.06	2.42	9.47

[a] Dilute acetate, and chloroacetate buffers employed in appropriate ranges of pH. The formation of the intermediate was followed at 280 mμ, its decomposition at 245 mμ.

propane.[8,15] The cross-conjugated carbonium ion derived from the diketal of *p*-benzoquinone should certainly be a great deal more stable than that derived from 2,2-dimethoxypropane and, hence, one might well have expected the former species to be very much the more reactive. The explanation for the opposite result is not clear. This observation does suggest that those factors which account for the related behavior observed with ortho esters may be important for the determination of reactivities of at least some ketals as well.

Experimental Section

We are indebted to Dr. Bernard Belleau for providing a sample of *p*-benzoquinone tetramethyl ketal.[14] The sample provided was recrystallized twice from petroleum ether (bp 60–80) prior to use in kinetic measurements, mp 44°. Kinetic measurements were performed spectrophotometrically with the aid of a Zeiss PMQ II spectrophotometer equipped with a thermostated cell holder through which water from a thermostated bath was continuously circulated. Formation of the reaction intermediate was followed at 280 and its decomposition at 245 mμ. All reactions were carried out at 25°, ionic strength 0.50, in aqueous solution containing 3% acetonitrile. First-order rate constants were calculated in the usual fashion and second-order rate constants by dividing the first-order constants by the activity of hydrogen ions. Values of pH were obtained with the aid of a Radiometer PHM 4c pH meter. Distilled water was employed throughout.

Registry No.—Tetramethyl ketal of *p*-benzylquinone 1579-103-4.

(15) The data for comparison, obtained by Kreevoy and Taft[8] refer to 50% dioxane solutions. Previous work in this laboratory (K. Koehler, unpublished observations) indicates that rates for reactions of the type of interest here are slowed by about an order of magnitude in 50% aqueous dioxane compared with water. This factor has been employed in arriving at the indicated rate ratio.

The Photocycloaddition of Diphenylacetylene to 2,3-Dihydropyran

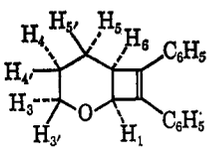
H. M. ROSENBERG AND PAUL SERVE

Air Force Materials Laboratory, Wright-Patterson Air Force Base, Ohio, and Wright State University, Dayton, Ohio

Received October 23, 1967

Cyclobutanes are frequently generated in photochemical reactions between olefins. Numerous examples of self-addition as well as cycloaddition between unlike olefins are encountered.[1-3] Reports of cyclobutene formation in the analogous reactions between acetylenes and olefins are confined almost exclusively to the cycloaddition of alkynes to α,β-unsaturated carbonyl compounds,[4-10] most of which require sensitization, although the photocycloaddition reaction between dimethylacetylene dicarboxylate and norbornene has recently been reported.[11] Reports of the participation of arylacetylenes in the photochemical synthesis of cyclobutenes are rare.[10,12]

During the course of our investigation of the photochemical behavior of acetylenes, we found that diphenylacetylene reacted smoothly with an excess of 2,3-dihydropyran to yield a 1:1 addition product upon irradiation at 2537 Å.



I

The product was characterized as the cyclobutene addition product (I), 7,8-diphenyl-2-oxabicyclo[4.2.0]-oct-7-ene, on the basis of spectral evidence presented in the Experimental Section.

An interesting feature of the nmr spectrum was the quartet at τ 6.90 instead of the expected octet. Based on a molecular model, we interpret this to reflect a 90° dihedral angle between H_6–C_6 and H_5–C_5.

In an attempt to gain information regarding the reactive excited species involved in the reaction between diphenylacetylene and 2,3-dihydropyran, quenching and sensitization experiments were performed. It was found that pyrene (triplet energy 48.7 kcal/mol[13]) inhibited the reaction between diphenylacetylene (triplet energy 51 kcal/mol[14]) and 2,3-dihydropyran. Equimolar concentrations of diphenylacetylene and quencher were used. Since their molar extinction coefficients are approximately equal at the excitation wavelength (log ε 4.1 at 2537 Å) the quenching effect was due to triplet energy transfer rather than absorption of the exciting light by pyrene. On the other hand, the reaction conducted in a pyrex vessel and irradiated at 3400 Å was successfully sensitized by triphenylene (triplet energy 66.6 kcal/mol[13]). The unsensitized reaction does not occur upon photolysis at this wavelength. We conclude that the reaction

(1) A. Mustafa, *Chem. Rev.*, **51**, 1 (1952).
(2) R. O. Kan, "Organic Photochemistry," McGraw-Hill Book Co., New York, N. Y., 1966.
(3) D. C. Neckers, "Mechanistic Organic Photochemistry," Reinhold Publishing Corp., New York, N. Y., 1967.
(4) P. E. Eaton, *Tetrahedron Lett.*, 3695 (1964).
(5) R. Criegee and H. Furrer, *Chem. Ber.*, **97**, 2942 (1964).
(6) R. Criegee, U. Zirngibl, H. Furrer, D. Seebach, and G. Freund, *ibid.*, **97**, 2949 (1964).
(7) D. Seebach, *ibid.*, **97**, 2953 (1964).
(8) R. L. Cargill, M. E. Beckham, A. E. Siebert, and J. Dorn, *J. Org. Chem.*, **30**, 3647 (1965).
(9) R. Askani, *Chem. Ber.*, **98**, 2322 (1965).
(10) S. P. Pappas and B. C. Pappas, *Tetrahedron Lett.*, 1597 (1967).
(11) M. Hara, Y. Odaira, and S. T. Tsutsumi, *Tetrahedron*, **22**, 95 (1966).
(12) O. L. Chapman and W. R. Adams, *J. Amer. Chem. Soc.*, **89**, 4243 (1967).
(13) W. G. Herkstroeter, A. A. Lamola, and G. S. Hammond, *ibid.*, **86**, 4537 (1964).
(14) M. Beer, *J. Chem. Phys.*, **25**, 745 (1956).

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]

TORLEIF UTNE, RONALD B. JOBSON, AND FREDERICK W. LANDGRAF

Merck Sharpe & Dohme Research Laboratories, Division of Merck & Co., Inc., Rahway, New Jersey

Received September 13, 1967

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).