3.82 (s, 6 H), 3.84 (s, 6 H), 4.75 (dd, J = 8 Hz, 2 H), 6.82–7.04 (m, 6 H); IR (KBr) 3400, 1650, 1510 cm^{-1}; mass spectrum, m/e (relative intensity) 448 (M^+, 4), 430 (23), 412 (22), 264 (13), 164 (100); high-resolution mass spectrum, calcd for $C_{22}H_{28}O_8N_2$ m/e 448.4718, found m/e 448.4668.

6,7-Dimethoxyisoquinoline (14a). To a refluxing solution of **12a** (1 g) in 40 mL of CH_3CN was added dropwise $POCl_3$ (2 mL) in 5 mL of CH_3CN. After 1 h, the mixture was cooled, the solvent evaporated, and the residue added to ice–water and then washed with ether. The aqueous layer was basified with concentrated NH_4OH and extracted with CH_2Cl_2. Chromatography furnished 0.628 g of **14a** (71%), mp 89–90 °C (lit.[14] mp 90–91 °C).

6-(Benzyloxy)-7-methoxyisoquinoline (14b). Following the procedure used to prepare **14a**, formamide **12b** was cyclized to **14b** (75%), mp 125–127 °C (lit.[15] mp 127–128 °C).

Acknowledgment. The Robert A. Welch Foundation and NATO (Grant No. RG158.80) are thanked for generous financial support. Dr. David Sawyer is thanked for a high-resolution mass spectrum.

Registry No. 2a, 78004-17-8; **2b**, 21857-14-7; **3a** (isomer 1), 78004-18-9; **3a** (isomer 2), 78004-19-0; **3b** (isomer 1), 78004-20-3; **3b** (isomer 2), 78004-21-4; **7**, 78004-22-5; **8**, 78004-23-6; **9**, 78004-24-7; **10**, 58-74-2; **11b**, 71146-40-2; **12a**, 78004-25-8; **12b**, 78004-26-9; **12c**, 58644-57-8; **13**, 78004-27-0; **14a**, 15248-39-2; **14b**, 78004-28-1; methyl isocyanide, 593-75-9; veratraldehyde, 120-14-9; (3,4-dimethoxyphenyl)acetyl chloride, 10313-60-7.

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Reduction of *gem*-Dibromides with Diethyl Phosphite

Toshikazu Hirao, Toshio Masunaga, Yoshiki Ohshiro,* and Toshio Agawa

Department of Petroleum Chemistry, Faculty of Engineering, Osaka University, 2-1 Yamada-Oka, Suita, Osaka 565, Japan

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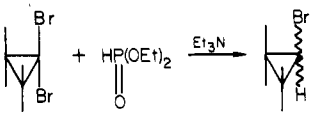
Much attention has been paid to the conversion of *gem*-dihalocyclopropanes to monohalocyclopropanes.[1] In most of dehalogenation reactions, however, reagents are limited to metallic ones such as organotin hydride,[1a] lithium aluminum hydride,[1b] sodium borohydride,[1c] Grignard reagent,[1d] and zinc–copper couple,[1e] and these methods have several disadvantages. Herein, we report a versatile reduction of *gem*-dibromo derivatives by using diethyl phosphite and triethylamine.

gem-Dibromocyclopropanes were treated with diethyl phosphite in the presence of triethylamine to give monobromocyclopropanes in good yields with the deposition of $Et_3N{\cdot}HBr$. Under the present reaction conditions, a further reduction of the resultant monobromide was not observed.



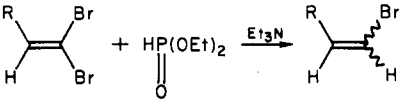
1

A variety of *gem*-dibromocyclopropanes were successfully reduced to the corresponding monobromides as shown in Table I. The dibromides, **1d** and **1e**, having an electron-withdrawing group were subject to the smooth debromination even at room temperature to produce the corresponding monobromocyclopropanes in 88% and 86% yields, respectively, without a chemical change of functional groups. This method could not be applied to the reduction of 7,7-dichloronorcarane (**1h**) under the same reaction conditions.

The absence of triethylamine apparently reduced the reduction yield, so triethylamine would play a significant part in the reaction. It was reported that dialkyl phosphite reacts with carbon tetrachloride in the presence of triethylamine to give dialkyl chlorophosphite and chloroform, in which the intermediate $(RO)_2PO^-$ was supported.[2] The same intermediate may be assumed in the present reaction path.

Dibromomalonamide has been reported to be reduced to malonamide with trialkyl phosphite in alcohol at room temperature.[3] By this method, however, 7,7-dibromonorcarane (**1f**) was not reduced, while the reduction of **1f** with diethyl phosphite and triethylamine occurred even at room temperature to produce the corresponding monobromide in 59% yield.

The present reduction method could be extended to the conversion of *gem*-dibromoalkenes into monobromoalkenes. β,β-Dibromostyrene (**2i**) reacted with 2 equiv of diethyl phosphite and triethylamine at room temperature for 4 h to give β-bromostyrene in 96% yield (trans/cis = 94:6). Similarly, the reduction of 1,1-dibromo-3-



methyl-4-phenyl-1,3-butadiene (**2k**) was performed to produce the corresponding monobromo diene, as shown in Table I. Since the dibromoalkenes are easily prepared from the aldehyde,[4] the present method is estimated as a convenient procedure for the preparation of 1-bromo-1-alkenes.

A similar reduction is expected in the reaction of *gem*-dibromoalkenes with trichlorosilane and triethylamine,[5] but the reaction of **2i** with 2 equiv of trichlorosilane and triethylamine at room temperature for 4 h gave β-bromostyrene in only 37% yield (trans/cis = 91:9).

Experimental Section

gem-Dibromocyclopropanes[6] and *gem*-dibromoalkenes[4] were prepared according to the reported procedures. Diethyl phosphite,

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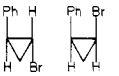
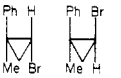
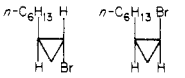
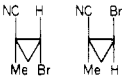
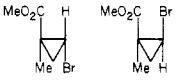
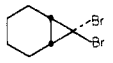
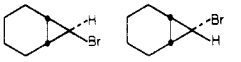
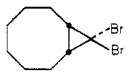
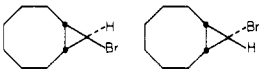
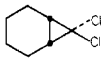
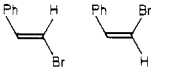
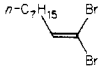
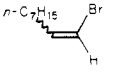
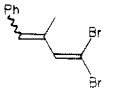
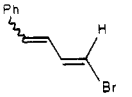
Table I. Reduction of *gem*-Dibromo Derivatives

1 or 2	HP(O)(OEt)$_2$, equiv	Et$_3$N, equiv	reacn condn: temp, °C	reacn condn: time, h	% yield	reduction products
 1a	4	2	90	5	93	 (75:25)
 1b	2	3	90	9	91	 (71:29)
 1c	3	3	90	5	86	 (35:65)
 1d	1.2	1.2	rt	0.5	88	 (25:75)
 1e	1.2	1.2	rt	24	86	 (55:45)
 1f						
	1.2	1.2	90	12	40	(19:81)
	2	4	90	6	83	(18:82)
	4	2	90	7	83	(17:83)
	4	2	rt	50	59	(12:88)
	4	0	90	12	13	(20:80)
 1g	4	2	90	5	74	 (22:78)
 1h	3	3	90	20		
 2i	2	2	rt	4	96	 (94:6)
 2j	2	2	rt	68	50[a]	
 2k	2	2	rt	24	60	

[a] Mixture of trans and cis isomers. The ratio could not be detemined.

trichlorosilane, and triethylamine are commercially available and purified by distillation.

Reduction of 1,1-Dibromo-2-phenylcyclopropane (1a) with Diethyl Phosphite. To a solution of 1.10 g (4.0 mmol) of 1,1-dibromo-2-phenylcyclopropane (**1a**) and 2.21 g (16.0 mmol) of diethyl phosphite was added 0.81 g (8.0 mmol) of triethylamine and the mixture was stirred at 90 °C for 5 h. Ether (50 mL) was added, and then Et$_3$N·HBr was removed by filtration. After evaporation of the filtrate, the residue was chromatographed on a silica gel column, eluting with *n*-hexane, to produce 1-bromo-2-phenylcyclopropane; yield 0.73 g (93%, trans/cis = 75:25).

The reduction of other *gem*-dibromocyclopropanes and *gem*-dibromoalkenes was carried out in the same manner. The reaction conditions and the amount of diethyl phosphite and triethylamine are shown in Table I. The products were identified by comparison of their IR and NMR spectra with those of authentic samples.

Reduction of β,β-Dibromostyrene with Trichlorosilane. To a solution of 1.05 g (4.0 mmol) of β,β-dibromostyrene (**2i**) and 1.08 g (8.0 mmol) of trichlorosilane in 2 mL of dichloromethane was added 0.81 g (8.0 mmol) of triethylamine in 1 mL of dichloromethane at 0 °C and the mixture was stirred at room temperature for 4 h. Ether (50 mL) was added, and then Et$_3$N·HBr was removed by filtration. After evaporation of the filtrate, the residue was chromatographed on a silica gel column, eluting with *n*-hexane, to produce β-bromostyrene; yield 0.27 g (37%, trans/cis = 91:9).

Acknowledgment. This work was carried out with Grant-in-aid for Scientific Research No. 543025 from the Ministry of Education.

Registry No. 1a, 3234-51-3; **1b**, 17343-73-6; **1c**, 41848-90-2; **1d**, 63262-97-5; **1e**, 39647-01-3; **1f**, 2415-79-4; **1g**, 1196-95-8; **1h**, 823-69-8; **2i**, 7436-90-0; **2j**, 39247-28-4; **2k**, 77295-77-3; diethyl phosphite, 762-04-9; *trans*-1-bromo-2-phenylcyclopropane, 32523-77-6; *cis*-1-bromo-2-phenylcyclopropane, 32523-76-5; *trans*-1-bromo-2-phenyl-2-methylcyclopropane, 72722-52-2; *cis*-1-bromo-2-phenyl-2-methylcyclopropane, 72722-55-5; *trans*-1-bromo-2-hexylcyclopropane, 34780-91-1; *cis*-1-bromo-2-hexylcyclopropane, 34780-90-0; *trans*-1-bromo-2-cyano-2-methylcyclopropane, 78004-14-5; *cis*-1-bromo-2-cyano-2-methylcyclopropane, 78004-15-6; methyl *trans*-2-bromo-1-methylcyclopropanecarboxylate, 58683-50-4; methyl *cis*-2-bromo-1-methylcyclopropanecarboxylate, 58683-51-5; (1α,6α,7β)-7-bromobicyclo[4.1.0]heptane, 1121-40-0; (1α,6α,7α)-7-bromobicyclo[4.1.0]-heptane, 1121-41-1; (1α,8α,9β)-9-bromobicyclo[6.1.0]nonane, 1551-95-7; (1α,8α,9α)-9-bromobicyclo[6.1.0]nonane, 1551-94-6; (*E*)-β-bromostyrene, 588-72-7; (*Z*)-β-bromostyrene, 588-73-8; (*E*)-1-bromonon-1-ene, 53434-75-6; (*Z*)-1-bromonon-1-ene, 39924-58-8; (*E*,X)-1-bromo-4-phenyl-3-methyl-1,3-butadiene, 78004-16-7.

Thio Analogues of Catechol Estrogens[1]

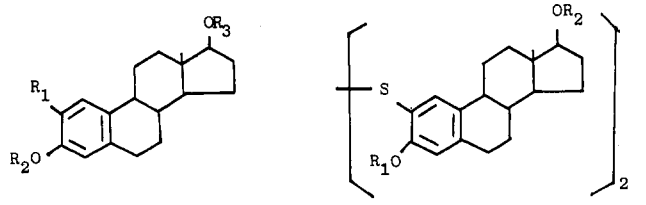
Shigeo Ikegawa[2] and Jack Fishman*

The Rockefeller University, New York, New York 10021

Received March 20, 1981

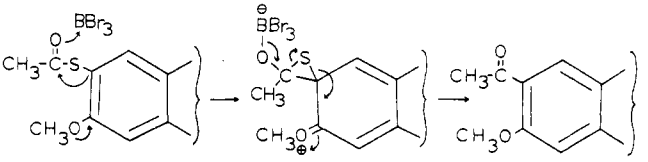
Catechol estrogens which contain a phenolic hydroxyl group at the C-2 position in addition to that originally present at C-3 are the dominant metabolites of estradiol in man and other mammalian species.[3,4] The principal catechol estrogen, 2-hydroxyestrone (2,3-dihydroxyestra-1,3,5(10)-trien-17-one), exhibits no conventional uterotropic activity[5] but does exert effects at the CNS or pituitary level.[6] A neuroendocrine role for the catechol estrogens is supported by their in situ formation in the brain and pituitary[7,8] and their action at these sites may be mediated by their biochemical interrelationships with the biogenic catecholamines. Thus, the catechol estrogens are excellent competitive inhibitors of the catechol *O*-methyltransferase mediated O-methylation of the catecholamines,[9] and they also have been demonstrated to inhibit tyrosine hydroxylase,[10] the rate-limiting enzyme of catecholamine biosynthesis. In order to probe the significance of these interactions, we sought to prepare derivatives of the catechol estrogens which would exhibit exaggerated effects on either one or both of these enzyme systems. In addition, these substances were desirable because of their potential as inhibitors of the brain estrogen-2-hydroxylase and hence as probes of the biological contribution of the catechol estrogens formed in the CNS.

Chart I



1. R_1 = H, R_2 = CH_3, R_3 = Ac
2. R_1 = SO_2Cl, R_2 = CH_3, R_3 = Ac
3. R_1 = SH, R_2 = CH_3, R_3 = H
4. R_1 = SAc, R_2 = CH_3, R_3 = Ac
5. R_1 = R_3 = Ac, R_2 = H
6. R_1 = CH_3, R_2 = H
7. R_1 = R_2 = H
8. R_1 = R_2 = Ac
9. R_1 = SAc, R_2 = R_3 = Ac

Scheme I



The initial structures to which we directed our synthetic efforts were those in which one or both of the phenolic groups of the catechol estrogen were replaced by thiol functions. The thiol derivatives were selected on the basis of a number of considerations including the recent report that a dopamine structure in which the meta phenolic group was replaced by a thiol function was an effective irreversible inhibitor of COMT.[11] A starting point in our synthesis of thiol derivatives of catechol estrogens was provided by the report that the electrophilic addition of chlorosulfonic acid to 17β-acetoxy-3-methoxyestra-1,3,5-(10)-triene (**1**, Chart I) results in the regioselective formation of the 2-chlorosulfonyl derivative which can be transformed to the 2-thiol by reduction with metal hydrides.[12,13] Utilizing the described procedure, we prepared 17β-acetoxy-2-(chlorosulfonyl)-3-methoxyestra-1,3,5(10)-triene (**2**), which was then reduced with lithium aluminum hydride ($LiAlH_4$) to yield the corresponding 2-thio derivative **3**. The material gave a positive response to Ellman's reagent, and it exhibited the signals for the C-1 and C-4 protons at 7.18 and 6.57 ppm, respectively, in the nuclear magnetic resonance (NMR) spectrum. Attempts at O-demethylation of **3** to provide the desired 2-mercapto-3-hydroxy product failed despite the use of O-demethylating reagents such as BBr_3 and 48% HBr in acetic acid, yielding only complex mixtures. With the expectation that protection of the thiol group would yield better results, the thiol derivative **3** was acetylated to provide the diacetate **4**, which was then subjected to O-demethylation with boron tribromide. This reaction also failed to yield the desired mercaptophenol. The product isolated contained no sulfur and was identified as 2-acetylestra-1,3,5(10)-triene-3,17β-diol 17-acetate (**5**) by means of its NMR spectrum as well

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(2) Visiting Fellow from Tohoku University, Aobayama, Sendai, 980, Japan.

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