

Wagner-Meerwein Rearrangement of Allylbenzene Derivatives. I. Bromination of Safrole¹⁾

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The reaction of safrole (I) with bromine (II) was examined giving different results from the literature,³⁾ *i.e.*, 2,3-dibromo-1-(3',4'-methylenedioxyphenyl)propane (III), 1,3-dibromo-2-(3',4'-methylenedioxyphenyl)propane (V) and their bromo-substituted derivatives (IV and VI) were obtained. The formation of rearranged adducts (V and VI) suggests that Wagner-Meerwein rearrangement occurred during this addition. The relationship between the reaction conditions and the ratio of the products was investigated.

Previously, we have found that the reaction of *N,N*-dibromobenzenesulfonamide with safrole gave the Wagner-Meerwein type rearranged addition products and their bromo-substituted compounds together with normal adducts.⁴⁾ During this study, we have found that a mixture of addition products of bromine to safrole was also produced as by-products in the reaction. In order to clarify the components of the mixture and confirm their structures, safrole (I) was allowed to react with bromine (II) according to the method described by Woy.³⁾ The reaction mixture was found to have similar components to the bromo-adducts in the reaction of *N,N*-dibromobenzenesulfonamide with safrole (I) by the comparison of nuclear magnetic resonance (NMR) spectra and retention time in gas chromatography. Our results of reinvestigation of this reaction demonstrated us a different conclusion from the literature.

Safrole (I) was made to react with bromine (II) in various molar ratios. The reaction of I with II in 1:1 molar ratio and that in 2:1 molar ratio gave similar oily products boiling at 171° (7 mmHg). The thin-layer chromatography (TLC) of this oil indicated that it was still a mixture of two components which had similar polarity. Careful separation of the oil by silica gel column chromatography resulted in formation of two kinds of oils, III, bp 151—152° (4 mmHg), and V, bp 170—171° (6 mmHg).

Contrary to these results, in the reaction of I with II in 1:2 molar ratio, a mixture of crystals (IV) and (VI) was produced together with III and V. Very close two spots were also detected on TLC of this crystalline mixture. Separation of IV and VI was successfully carried out by repeated fractional crystallization.

In order to establish the structures of III, IV, V and VI, reductive debrominations of them with lithium aluminum hydride were performed. The same oil (VII, bp 59°/19 mmHg) was obtained from III and IV, and another oil (VIII, bp 135—140°/25 mmHg-bath temperature) was obtained from V and VI. The NMR spectral data of these products indicate that VII has *n*-propyl side chain and VIII has isopropyl one. Furthermore, VII and VIII were identified with the authentic samples⁵⁾ of 1-(3',4'-methylenedioxyphenyl)propane and 2-(3',4'-

1) A brief communication of this work was presented at the 94th Annual Meeting of the Pharmaceutical Society of Japan, Sendai, April, 1974.

2) Location: Kowakae, Higashi-osaka, Osaka.

3) R. Woy, *Arch. Pharm.*, **228**, 37 (1890).

4) K. Otsuki and T. Irino, *Chem. Pharm. Bull.* (Tokyo), **23**, 482 (1975).

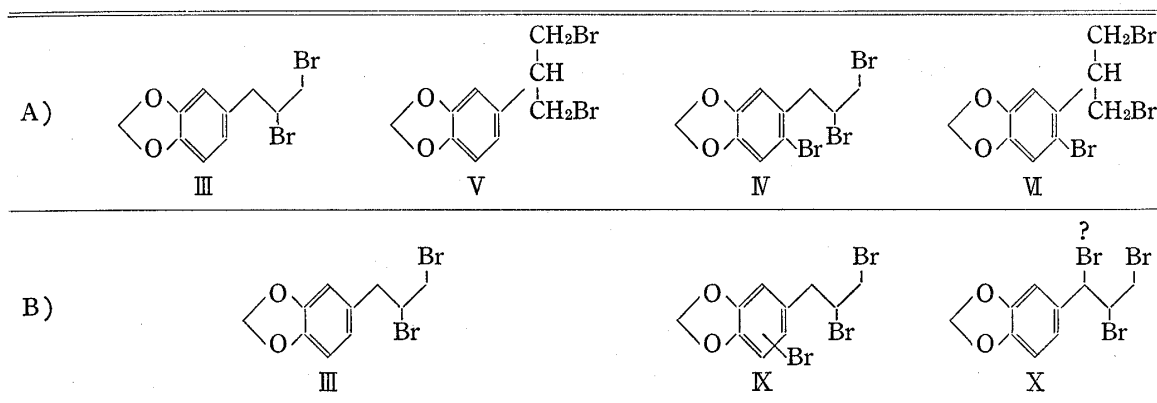
5) G. Ciamician and P. Silber, *Chem. Ber.*, **23**, 1162 (1890); R.L. Shriner and E.C. Kleiderer, "Organic Syntheses," Coll. Vol. II, ed. by A.H. Blatt, John Wiley and Sons, Inc., New York, N.Y., 1943, p. 538; E. Oertly and Ame Pictet, *Chem. Ber.*, **43**, 1336 (1910); A. Behal, *Bull. Soc. Chim.*, **3**, 732 (1908); A. Behal and M. Tiffeneau, *Compt. Rend.*, **141**, 596 (1905) [*Beil.* **H19**, 30].

methylenedioxyphenyl)propane, respectively, by comparison of their TLC, infrared (IR) spectra and NMR spectra.

Therefore, it is conclusive that III is 2,3-dibromo-1-(3',4'-methylenedioxyphenyl)propane and V is 1,3-dibromo-2-(3',4'-methylenedioxyphenyl)propane. Crystals, IV, are presumed as a derivative of III substituted by a bromine atom at the C6-position of phenyl group, and crystals, VI, as similar one of V, from the comparison of integral values of aromatic protons and patterns of all signals of NMR spectra of III, IV, V and VI. Mass spectral data of IV and VI also strongly support these presumptions.

Woy³⁾ described that the bromination of safrole gave three kinds of compounds, an oil, bp 215° (22 mmHg), "2,3-dibromo-1-(3',4'-methylenedioxyphenyl)propane" (III), crystals, mp 54°, so called "2,3,x-tribromo-1-(3',4'-methylenedioxyphenyl)propane" (IX) and crystals, mp 87°, "1(?),2,3-tribromo-1-(3',4'-methylenedioxyphenyl)propane" (X). However, it is now apparent that Woy's oil is a mixture of III and V, the crystals (mp 54°, IX) are assigned to IV, and the crystals (mp 87°, X) are assigned to VI, as shown in Table I.

TABLE I. Products of the Reaction of Safrole (I) with Bromine (II)



A) The structures of the products were put forward by the present authors.

B) The structures of the products were put forward by Woy.

The formation of abnormal adducts, V and VI, suggests that Wagner-Meerwein rearrangement occurred during the reactions. In order to find the relationship between components of the products and the reaction conditions, the reaction of I with II was examined under various conditions. Some of the results were shown in Table II and Table III.

First, the relationship between the ratio of the rearranged products (V and VI) to the normal products (III and IV) and the reaction conditions was examined. Temperature seemed to have marked influence on the ratio of the products at the higher region in any ratio of I/II, thus the ratio of the rearranged products increased at 61°. In lower temperature, however, the ratio of the rearranged products varied irregularly (Table II).

In equimolar reactions, it is interesting that from lower and higher concentrations of starting materials, the ratios V/III are increased, while in the moderate concentrations, the ratios are relatively decreased (Table III).

Next, we have investigated the influences of the molar ratios and concentrations of starting materials (I and II) on the ratio of unsubstituted to bromo-substituted products (III+V/IV+VI). When the molar ratio of I: II was taken at 1:1, it was found that no bromo-substituted products were formed under low concentrations (below 10%) of starting materials, while when the concentrations of them were over 10%, a small amount of the bromo-substituted products were obtained (Table III). In spite of using 1:2 molar ratio of I/II, the unsubstituted products (III and V) were obtained (Table II). At the higher temperature (61°), the following results were appeared because of bromine (II) may be escaped from the reaction system; (i) the proportion of the bromo-substituted products was smaller than that at

TABLE II. Influence of Reaction Temperature and Molar Ratio of I to II on the Ratio of the Reaction Products (III, IV, V and recovered I)

	Temperature	The ratio of the reaction products				
		III	V	IV	VI	I
A	-10—-7°	31	9	0	0	59
	-2—0°	32	12	0	0	55
	14—16°	31	13	0	0	56
	61°	19	14	0	0	65
B	-10—-7°	71	26	0	0	3
	-2—0°	71	22	0	0	7
	14—16°	73	27	0	0	0
	61°	46	32	0	0	20
C	-10—-7°	13	19	62	6	0
	-2—0°	7	20	66	7	0
	14—16°	9	20	62	9	0
	61°	30	37	26	7	0

reaction conditions

concentration: I; 4 g/100 ml CHCl₃, II; 8 g/100 ml CHCl₃

A: molar ratio of I to II; 2:1

B: molar ratio of I to II; 1:1

C: molar ratio of I to II; 1:2

TABLE III. Influence of Concentration on the Ratio of the Reaction Products (III, V, IV plus VI and recovered I)

g/100 ml CHCl ₃		The ratio of the reaction products			
I	II	III	V	IV plus VI	I
0.1	0.1	40	30	0	18 ^{a)}
0.5	0.5	57	40	0	1 ^{a)}
1.0	1.0	62	29	0	4 ^{a)}
1.6	1.6	71	29	0	0
4.0	8.0	73	27	0	0
4.0	16	70	30	0	0
16	16	64	33	3	0
32	32	57	39	3	1
50	50	49	41	7	2
100	100	36	35	12	16 ^{a)}
200	200	35	37	12	15 ^{a)}

^{a)} Several products having shorter retention times were detected.

reaction conditions

temperature; at 14—16°

molar ratio of I to II; 1:1

the other temperatures (case C in Table II), (ii) the safrole (I) was recovered more than that at the other temperatures (case A and B in Table II).

The third problem is the ratio of the normal to the rearranged product (IV/VI) in so-called bromo-substituted products. The comparison was made in the reaction of 1:2 molar ratio of I/II. The ratio of IV/VI was shown in Table II. This ratio was larger than it of III/V (case A and B). This fact may be ascribed to the different rates of bromo-substitution of III and V. Aside from above observation, a mixture of III and V (71:29 molar ratio) was allowed to react with bromine to give predominant yield of IV, and considerable amount of V was recovered. It seems that the poor reactivity of V is caused by the steric effect of neighboring isopropyl side chain in the bromo-substitution.

Conclusively, although normal addition was rather preferential in the all conditions, contents of the rearranged products increased in higher temperature and in relatively high or low concentration of starting materials.

It seemed that the addition of bromine or pseudo-bromine to aromatic compound having allyl group in its side chain such as safrole cause Wagner-Meerwein type rearrangement to some extent. Accordingly, the reaction with other allyl compounds will be reported in later paper.

Experimental⁶⁾

Reaction of Safrole (I) with Bromine (II)—A solution of II (0.8 g, 0.005 mole) in CHCl_3 (10 ml) was dropwise added to cooled ($14\text{--}16^\circ$) and stirred mixture of I (0.81 g, 0.005 mole) and CHCl_3 (20 ml) in a period of 0.5 hr to 1 hr. After the addition of the solution, the stirring was continued for additional 2 hr at room temperature. After the reaction mixture was allowed to stand overnight, the CHCl_3 solution was evaporated under reduced pressure, and the residual oil was distilled, bp 171° (7 mmHg). The oil was dissolved in hexane, and charged on a column of silica gel. Elution with hexane gave 2,3-dibromo-1-(3',4'-methylenedioxyphenyl)propane (III) (1.12 g), bp $151\text{--}152^\circ$ (4 mmHg). *Anal.* Calcd. for $\text{C}_{10}\text{H}_{10}\text{O}_2\text{Br}_2$: C, 37.30; H, 3.13. Found: C, 37.32; H, 3.01. NMR (CDCl_3) δ : 6.74 (3H, singlet, arom.), 5.93 (2H, singlet, $-\text{O}-\text{CH}_2-\text{O}-$), 4.30 (1H, multiplet, $-\text{CHBr}-$), 2.80–3.96 (4H, multiplet, $\text{Ph}-\text{CH}_2-$, $-\text{CH}_2\text{Br}$).

From the second fraction eluted with hexane, 1,3-dibromo-2-(3',4'-methylenedioxyphenyl)propane (V) (0.41 g), bp $170\text{--}171^\circ$ (6 mmHg) was obtained. *Anal.* Calcd. for $\text{C}_{10}\text{H}_{10}\text{O}_2\text{Br}_2$: C, 37.30; H, 3.13. Found: C, 37.51; H, 3.10. NMR (CDCl_3) δ : 6.72 (3H, singlet, arom.), 5.98 (2H, singlet, $-\text{O}-\text{CH}_2-\text{O}-$), 3.04–3.86 (5H, multiplet, $-\text{CH}\begin{matrix} \text{CH}_2\text{Br} \\ \text{CH}_2\text{Br} \end{matrix}$).

Reaction of I with II in 1:2 Molar Ratio—A solution of II (1.6 g, 0.01 mole) in CHCl_3 (20 ml) was dropwise added to cooled ($14\text{--}16^\circ$) and stirred solution of I (0.81 g, 0.005 mole) in CHCl_3 (20 ml) in a period of 1 hr. Then the mixture was treated with the similar manner described above. Elution of the column with hexane gave III (0.05 g) in the first fraction. Subsequent elution gave an oil V (0.30 g). From the third fraction eluted with hexane, colorless crystals consisted of IV and VI were obtained. Isolation of them was carried out by fractional crystallization from hexane. Crystals, IV (1.22 g), mp $49\text{--}50^\circ$ (from hexane) were obtained as a slightly soluble component. *Anal.* Calcd. for $\text{C}_{10}\text{H}_9\text{O}_2\text{Br}_3$: C, 29.96; H, 2.26. Found: C, 29.90; H, 2.07. NMR (CDCl_3) δ : 6.95 (1H, singlet, arom.), 6.77 (1H, singlet, arom.), 5.97 (2H, singlet, $-\text{O}-\text{CH}_2-\text{O}-$), 4.40 (1H, multiplet, $-\text{CHBr}-$), 2.71–4.01 (4H, multiplet, $\text{Ph}-\text{CH}_2-$, $-\text{CH}_2\text{Br}$). Mass Spectrum m/e : 398, 400, 402, 404 (M^+), 319, 321, 323 (M^+-Br), 240, 242, (M^+-2Br), 213, 215 ($\text{M}^+-\text{CHBrCH}_2\text{Br}-\text{H}$). Crystals, VI (0.17 g), mp $86\text{--}87^\circ$ (from hexane) were obtained as a readily soluble component from the mixture. *Anal.* Calcd. for $\text{C}_{10}\text{H}_9\text{O}_2\text{Br}_3$: C, 29.96; H, 2.26. Found: C, 29.99; H, 2.26. NMR (CCl_4) δ : 7.00 (1H, singlet, arom.), 6.70 (1H, singlet, arom.), 5.99 (2H, singlet, $-\text{O}-\text{CH}_2-\text{O}-$), 3.72 (5H, multiplet, $-\text{CH}\begin{matrix} \text{CH}_2\text{Br} \\ \text{CH}_2\text{Br} \end{matrix}$). Mass Spectrum m/e : 398, 400, 402, 404 (M^+), 305, 307, 309 ($\text{M}^+-\text{CH}_2\text{Br}$), 212, 214 ($\text{M}^+-2\text{CH}_2\text{Br}-\text{H}$).

Reaction of I with II in 2:1 Molar Ratio—I (0.81 g, 0.005 mole) in CHCl_3 (20 ml) was allowed to react with II (0.4 g, 0.0025 mole) in CHCl_3 (5 ml) by the similar procedure described above giving III (0.36 g), V (0.15 g) and I (0.65 g).

Reduction of III, IV, V and VI with LiAlH_4 , Formation of VII and VIII—i) III (0.5 g) was mixed with LiAlH_4 (0.1 g) and anhydrous tetrahydrofuran (THF) (20 ml). The mixture was refluxed on a hot plate for 5 hr. Upon cooling, LiAlH_4 was decomposed by addition of H_2O . The mixture was acidified with 10% HCl and THF was evaporated *in vacuo*, and the residue was extracted with CH_2Cl_2 . The CH_2Cl_2 extract was dried over Na_2SO_4 and the solvent was evaporated *in vacuo* to leave 1-(3',4'-methylenedioxyphenyl)propane (VII) (0.25 g), bp 59° (19 mmHg). NMR (CDCl_3) δ : 6.63 (3H, singlet, arom.), 5.83 (2H, singlet, $-\text{O}-\text{CH}_2-\text{O}-$), 2.49 (2H, triplet, $\text{Ph}-\text{CH}_2-$, $J=8.0$ Hz), 1.52 (2H, multiplet, $-\text{CH}_2-$), 0.92 (3H, triplet, $-\text{CH}_3$, $J=7.0$ Hz).

ii) IV was reduced with LiAlH_4 by a similar manner as above giving VII.

iii) Same product, 2-(3',4'-methylenedioxyphenyl)propane (VIII), was obtained from V and VI on reducing with LiAlH_4 in a similar manner described above, bp $135\text{--}140^\circ$ (25 mmHg) (bath temperature). NMR (CDCl_3) δ : 6.66 (3H, singlet, arom.), 5.84 (2H, singlet, $-\text{O}-\text{CH}_2-\text{O}-$), 2.82 (1H, quintet, $-\text{CH}<$, $J=7.0$ Hz), 1.21 (6H, doublet, $-\text{CH}_3$, $J=7.0$ Hz).

6) Melting and boiling points are uncorrected. NMR spectra were measured with a type R-20-B 60 MHz Hitachi Perkin-Ermer spectrometer using TMS as an internal standard, Mass Spectra were measured on a type LKB-9000 Shimadzu Gas Chromatography Mass Spectrometry System, and GLC was performed on a Shimadzu model GC-3BT with a thermal conductivity detector.

Measurement of the Ratio of III, IV, V and VI—I was made to react with II in various molar ratios, temperatures and concentrations, as shown in Table II and Table III. The reaction mixtures were left overnight at the each reaction temperatures and treated with 10% aqueous Na_2CO_3 . The CHCl_3 solutions were applied to gas chromatographies under the following conditions: sample, 1—2 μl ; column, Silicon OV-1 chromosorb W (60—80 mesh), 2 m, 3 ϕ , glass column, 160°; carrier gas, hydrogen; gas flow rate, 30 ml/min. The peaks of III, V and the mixture of IV and VI were detected showing t_R : III, 10.8 min; V, 11.8 min; the mixture of IV and VI, 28.5 min, and the weight ratios of these were corrected by usual method. The ratio of IV and VI in the mixture was estimated from integral values of NMR spectra.

Reaction of the Mixture of III and V with II—A solution of the mixture of III and V (1.6 g) (III; 71%, V; 29%) in CHCl_3 (20 ml) was allowed to react with a solution of II (0.8 g) in CHCl_3 (20 ml) by the same manner described above. The ratio of the resulting products was measured by gas chromatography and NMR spectrometry to give III: V: IV: VI=3: 12: 68: 17.