2-(4′-Methoxyphenyl)-2-methoxyethanol[1]

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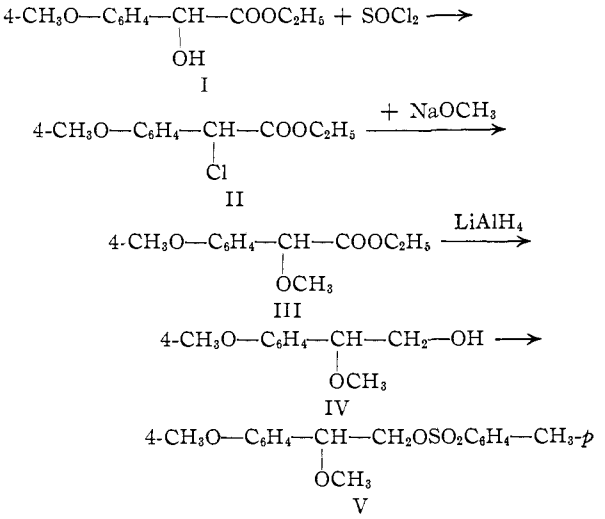
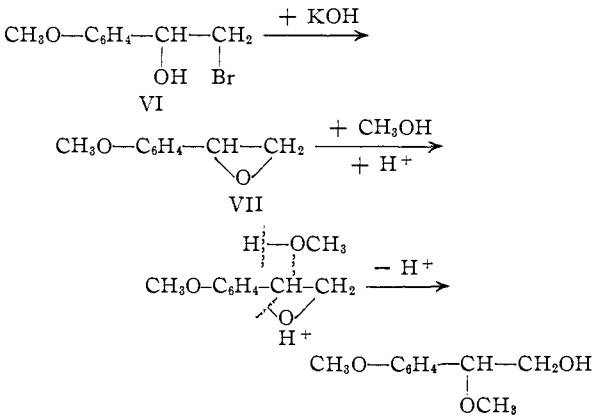
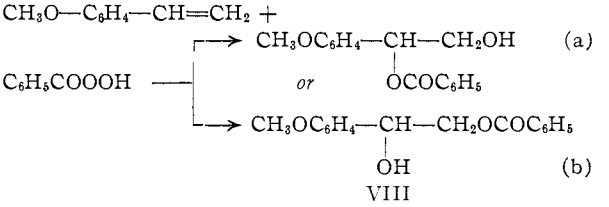
2-(4′-Methoxyphenyl)-2-methoxyethanol was prepared by two different procedures: (1) ethyl 4-methoxymandelate (I) was treated with thionyl chloride to give ethyl 4-methoxyphenylchloroacetate (II), which was converted into ethyl 4-methoxyphenyl-methoxyacetate (III) by treating it with a solution of sodium methoxide in methyl alcohol. Reduction of the latter ester III, or the acid, with lithium aluminum hydride gave 2-(4′-methoxyphenyl)-2-methoxyethanol (IV), which was converted into the *p*-toluenesulfonate (V) in the usual manner.



(2) 4-Methoxystyrene dibromide was hydrolyzed with aqueous acetone to the bromohydrin (VI), which was treated with alcoholic potassium hydroxide to give 4-methoxystyrene oxide (VII). This gave with methyl alcohol acidified with few drops of concentrated sulfuric acid 2-(4′-methoxyphenyl)-2-methoxyethanol.



Attempted synthesis of the oxide VII by the action of perbenzoic acid on 4-methoxystyrene resulted in the isolation of the benzoate of 1-(4′-methoxyphenyl)-ethanediol-1,2 (VIII a or b) which was identified as its tosylate.



Experimental

(Melting points were not corrected.)

Ethyl 4-Methoxyphenylchloroacetate.—*p*-Methoxymandelic ester[2] (30 g., *ca.* 0.143 mole) was cooled in ice, treated slowly with distilled thionyl chloride (25 g., 0.21 mole), and allowed to stand at room temperature for 3 days. The excess thionyl chloride was evaporated at room temperature, and the last traces were completely removed by the addition of dry ether and evaporation several times. The product was distilled in a vacuum to give **ethyl 4-methoxyphenylchloroacetate** as a colorless oil, b.p. 145–146° (4.5 mm.) (18 g.). The distillation should be carried out very carefully and at a very low pressure to minimize polymerization.

Anal. Calcd. for $C_{11}H_{13}O_3Cl$: C, 57.76; H, 5.73; Cl, 15.54. Found: C, 57.70; H, 5.73; Cl, 15.54.

Ethyl 4-Methoxyphenylmethoxyacetate (III).—Ethyl 4-methoxyphenylchloroacetate (18 g., *ca.* 0.079 mole) was treated at room temperature with a solution of sodium methoxide (from 2.1 g. of sodium, *ca.* 0.09 atom) in methyl alcohol (70 ml.), and allowed to stand overnight. The reaction mixture was diluted with ice-water, and extracted several times with ether, and dried (Na_2SO_4). The product was distilled in a vacuum to give **ethyl 4-methoxyphenylmethoxyacetate** as a colorless oil, b.p. 149–150° (5 mm.) (*ca.* 11 g.).

Anal. Calcd. for $C_{12}H_{16}O_4$: C, 64.3; H, 7.2. Found: C, 64.15; H, 6.95.

The aqueous solution was evaporated to dryness, and treated with a few ml. of ice-cold dilute hydrochloric acid. Extraction with ether gave an acid (*ca.* 3 g.), which was identical with that obtained by the hydrolysis of the above ester. It was crystallized from benzene–light petroleum to give **4-methoxyphenylmethoxyacetic acid** in colorless crystals, m.p. 70–71° (shrinking at 67°).

Anal. Calcd. for $C_{10}H_{12}O_4$: OCH_3, 31.6. Found: OCH_3, 30.1.

When the crude chloro compound was used without distillation, it gave the same product. However, the acid was impure, and was purified by dissolving it in ether and re-extracting with sodium carbonate solution (norite). In other runs the ratio of the ester to the acid was different but the total yield was the same.

2-(4′-Methoxyphenyl)-2-methoxyethanol (IV).—A solution of ethyl 4-methoxyphenylmethoxyacetate (14 g.) in dry ether (200 ml.) was slowly added to a suspension of lithium aluminum hydride (5 g.) in dry ether (200 ml.). The mixture was gently refluxed for 1.5 hr., cooled in ice, and the excess hydride was decomposed with the dropwise addition of alcohol. The reaction mixture was acidified with cold dilute hydrochloric acid, and the product extracted with ether. Removal of the ether left an oil which was refluxed with alcoholic potassium hydroxide for 1 hr., the alcohol evaporated, the residue diluted with water, extracted with ether and dried. Evaporation of the ether left a light yellow colored oil (10 g.) which was purified either by crystallization from benzene–light petroleum (b.p. 30–60°), or by distillation in a vacuum to give **2-(4′-methoxyphenyl)-2-methoxyethanol** as a colorless oil, b.p. 137–139° (5.5 mm.), which solidified to a colorless solid, m.p. 42–43° (shrinking at 40°).

Anal. Calcd. for $C_{10}H_{14}O_3$: C, 65.87; H, 7.75. Found: C, 64.92; H, 7.68.

The acid could be used instead of the ester to give the same product in the same yield. The ***p*-toluenesulfonate**, prepared from the alcohol (6 g.), *p*-toluenesulfonyl chloride (7.5 g.) and pyridine (15 ml.) in the usual manner, was

(1) This work was carried out by the author during his stay at U.C.L.A. as a Fulbright-Smith Mundt Scholar (Exchange-Visitor Program).

(2) E. Knorr, *Ber.*, **37**, 3173 (1904).

crystallized from benzene–light petroleum in colorless crystals, m.p. 71–72°.

Anal. Calcd. for $C_{17}H_{20}O_5S$: C, 60.7; H, 6.0; S, 9.52; OCH_3, 18.45. Found: C, 60.57; H, 6.16; S, 10.87; OCH_3, 17.0.

4-Methoxystyrene.—A mixture of 4-methoxycinnamic acid (50 g.), pure quinoline (150 ml.) and copper powder (5 g.) was slowly distilled in such a rate that a drop distilled over every 2 seconds. The distillate was dissolved in ether, extracted with ice-cold dilute hydrochloric acid, then with cold sodium carbonate solution, and dried (Na_2SO_4). Ether was evaporated in a nitrogen atmosphere, and the product distilled in a vacuum to give 4-methoxystyrene as a colorless oil, b.p. 51–52° (1 mm.)[3] (23–25 g.).

4-Methoxystyrene Bromohydrin (VI).—A solution of 4-methoxystyrene dibromide (20 g.) [prepared according to Guss,[6] using carbon tetrachloride instead of ether and chloroform] in acetone (100 ml.) was diluted with water (100 ml.) and stirred for 1 hour at room temperature. Water (200 ml.) was added, and the mixture extracted with ether, washed with cold dilute sodium hydrogen carbonate solution, and dried (Na_2SO_4). Ether was evaporated at room temperature to leave a pale yellow oil, which could not be purified by distillation as it was decomposed on heating (yield nearly quantitative).

4-Methoxystyrene Oxide (VII).—The bromohydrin (10 g., *ca.* 0.0435 mole) was dissolved in methyl alcohol (50 ml.) and treated with a solution of potassium hydroxide (2.5 g., *ca.* 0.446 mole) in methyl alcohol (50 ml.). The mixture was allowed to stand for 10–15 minutes with occasional shaking. It was diluted with ice-cold water, extracted with ether, and dried (K_2CO_3). The removal of the ether at room temperature in a nitrogen atmosphere left a nearly colorless oil, which solidified when cooled in ice and melted at room temperature. The product might be a mixture of the oxide and its dimerization product, the dioxane, and being unstable could not be purified by vacuum distillation.[4]

2-(4′-Methoxyphenyl)-2-methoxyethanol (IV).—The oxide (5 g.) was dissolved in methyl alcohol (25 ml.) containing two drops of concentrated sulfuric acid. The mixture was allowed to stand at room temperature for 2 hours, diluted with water, extracted with ether, washed with sodium hydrogen carbonate, and dried (Na_2SO_4). Evaporation of the ether left an oil which could not be obtained in a crystalline form by crystallization (*cf.* first method). It was repeatedly extracted with hot light petroleum (b.p. 30–60°), and separated from the insoluble fraction by decantation. The solvent was evaporated at room temperature and the remaining alcohol (*ca.* 3 g.) was converted into the tosylate in the usual manner. The product (*ca.* 3.5 g.) was pressed on a piece of unglazed clay to remove traces of a low melting material. It was crystallized from benzene–light petroleum (b.p. 30–60°) to give colorless crystals, m.p. 71–72°, undepressed on admixture with an authentic specimen.

Anal. Calcd. for $C_{17}H_{20}O_5S$: C, 60.7; H, 6.00; S, 9.52. Found: C, 61.22; H, 6.27; S, 8.5.

Action of Perbenzoic Acid on 4-Methoxystyrene.—A stirred solution of perbenzoic acid (11.8 g., 0.086 mole) in chloroform (100 ml.) was cooled in a freezing mixture and treated dropwise with a solution of 4-methoxystyrene (11.0 g., 0.082 mole) in chloroform (50 ml.). The temperature was not allowed to rise above 0°. After the addition was completed, the mixture was kept in a freezing mixture for one hour, then allowed to stand in a refrigerator for 24 hours. The chloroform solution was washed with cold potassium carbonate solution to remove the benzoic acid, dried (Na_2SO_4), and the chloroform removed under reduced pressure. The product was distilled in a vacuum, and the fraction which boiled at 70° (3 mm.) was rejected. Distillation was interrupted and the residue (*ca.* 10 g.) which failed to solidify was treated with *p*-toluenesulfonyl chloride (10 g.) in pyridine (10 ml.), left overnight and worked up as usual. On crystallization from methyl alcohol the **tosylate of 1-(4′-methoxyphenyl)-ethanediol-1,2 monobenzoate** was obtained in nearly colorless crystals, m.p. 113–114°.

Anal. Calcd. for $C_{23}H_{22}O_6S$: C, 64.78; H, 5.20; S, 7.51. Found: C, 64.54; H, 5.26; S, 7.65.

On hydrolysis of the benzoate with alcoholic alkali it gave benzoic acid and 1-(4′-methoxyphenyl)-ethanediol-1,2, m.p. 81–82°. Fodor and Kovács[5] gave m.p. 82°.

Anal. Calcd. for $C_9H_{12}O_3$: C, 64.25; H, 7.20. Found: C, 63.8; H, 7.31.

(3) C. Walling and K. B. Wolfstirn, THIS JOURNAL, **69**, 852 (1947).

(4) C. O. Guss, *ibid.*, **74**, 2562 (1952).

(5) G. Fodor and Ö. Kovács, *ibid.*, **71**, 1047 (1949).

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Acetylation and S-Alkylation of Ethylene Thiourea[1]

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Although a number of alkylisothioureas have been reported,[3] few S-alkyl derivatives of ethylene thiourea (2-alkylmercapto-2-imidazolines) are known. The methyl,[4] ethyl[4] and carboxymethyl derivatives[5] were prepared some years ago. Recently a series of substituted 2-benzylmercaptoimidazolines were synthesized by Easton, Hlynsky and Foster.[6a] This paper reports the preparation of a series of 2-alkylmercapto-2-imidazolines. The impure salts tended to be hygroscopic. Perhaps for this reason numerous attempts to prepare the amyl derivative yielded only crude material melting at about 60°. The compounds that were prepared are shown in Table I.

About a year after the present work was done, two reports[6a,b] cited the melting point of the benzyl derivative as 172°. Redetermination of the melting point indicated that our sample had undergone transformation to the 172° isomer upon long standing. We subsequently found an earlier report confirming the 147° melting point.[6c] The polymorphism which Donleavy noted for S-benzylthiuronium chloride[7] appears to hold for 2-benzylmercaptoimidazoline hydrochloride. The alkyl derivatives, like ethylene thiourea itself, are slowly decomposed by prolonged heating with acid or alkali, to yield, at least in part, the corresponding mercaptan. The bases tend to be unstable, hygroscopic and not easily crystallizable. The pK_a of the butyl derivative was found by potentiometric titration of the hydrobromide salt with alkali to be 9.0.

Attempts to condense ethylene thiourea with β-chloropropionitrile, β-chloro- or β-bromopropionic acid, or corresponding esters were without success although ethyl chloroacetate reacted easily. From the condensation of ethylene chlorobromide with ethylene thiourea, I and II were obtained, m.p. 167° and about 270°, respectively. I, which contained chlorine and bromine and had the correct carbon and hydrogen content, was converted to a base, m.p. 64°, containing chlorine but not bromine.

(1) This work was carried out principally in 1950 under a grant from the Research Corp., and was presented at the A.C.S. Meeting in Miniature, Phila., Jan. 29, 1953.

(2) Pharmacology Section, Sharp & Dohme Division, Merck & Co., Inc., West Point, Pa.

(3) T. B. Johnson and J. M. Sprague, THIS JOURNAL, **58**, 1348 (1936).

(4) W. Schacht, *Arch. Pharm.*, **235**, 451 (1897).

(5) T. B. Johnson and C. O. Edens, THIS JOURNAL, **63**, 3527 (1941); *ibid.*, **64**, 2706 (1942).

(6) (a) N. R. Easton, A. Hlynsky and H. Foster, *ibid.*, **73**, 3507 (1951); (b) S. R. Aspinall and E. J. Bianco, *ibid.*, **73**, 602 (1951); (c) J. Walker, *J. Chem. Soc.*, 1996 (1949).

(7) J. J. Donleavy, THIS JOURNAL, **58**, 1004 (1936).