aniline[10] in 1250 ml. of 95% ethanol was treated with 18.51 g. (0.19 mole) of concentrated hydrochloric acid and 18.25 g. of potassium thiocyanate in 50 ml. of water. The resulting solution was heated under reflux for two hours, cooled, then poured into two liters of water containing 20 ml. of concentrated ammonium hydroxide. Separation of the product by filtration yielded 45.5 g. of crude 1,4-diphenyl-2-thiolimidazole. Crystallization of the product from ethanol gave 31.0 g. (65%) of the desired thiol, m. p. 214–216°. A mixture with the thiol obtained from the cleavage of 1,4-diphenyl-2-benzylthioimidazole (VI) melted at 215–217°.

1,4-Diphenyl-2-methylthioimidazole (VIII) from 1,4-Diphenyl-2-thiolimidazole (IX).—A solution of 5.04 g. (0.02 mole) of 1,4-diphenyl-2-thiolimidazole, prepared from N-phenacylaniline, 2.84 g. (0.02 mole) of methyl iodide and 0.80 g. of sodium hydroxide in 160 ml. of 90% ethanol was heated under reflux for one hour. The yellow oil remaining after the removal of the solvent was extracted with 25 ml. of water and 25 ml. of benzene. On extraction of the benzene solution with dilute (1:5) hydrochloric acid, a green oil, insoluble in benzene and hydrochloric acid, separated. This was dissolved in the minimum amount of ethanol and the solution was poured into 100 ml. of water containing 10 ml. of concentrated ammonium hydroxide. The oil which separated solidified when stirred. In this way 3.23 g. (61%) of 1,4-diphenyl-2-methylthioimidazole, m. p. 63–66.5°, was obtained. Crystallization from dilute ethanol raised the melting point to 64–66°. This material was identical with that obtained by the condensation of phenacyl bromide with N-phenyl-S-methylisothiourea.

1,4-Diphenyl-2-benzylthioimidazole (VI) from 1,4-Diphenyl-2-thiolimidazole (IX).—1,4-Diphenyl-2-thiolimidazole (5.04 g.), prepared from N-phenacylaniline, was alkylated with benzyl chloride and the product isolated as described in the preceding experiment. Crystallization of the product from dilute alcohol yielded 2.75 g. (40%) of the desired 1,4-diphenyl-2-benzylthioimidazole, m. p. 69–70°. A mixed melting point determination proved that this compound was identical with the product from the condensation of N-phenyl-S-benzylisothiourea with phenacyl bromide.

Summary

1. The condensation of N-substituted-S-alkylisothioureas with phenacyl bromide produced 1-substituted-2-alkylthio-4-phenylimidazoles. No 1-substituted-2-alkylthio-5-phenylimidazoles were isolated from these reactions.

2. The structures of the imidazoles were established either by degradation to a known imidazole or by independent synthesis.

3. Red phosphorus and iodine in glacial acetic acid cleaved the 2-alkylthioimidazoles to 2-thiolimidazoles. Both benzyl and methyl groups were removed in this way.

MINNEAPOLIS 14, MINNESOTA RECEIVED AUGUST 22, 1949

(10) A. Bischler, *Ber.*, **25**, 2860 (1892).

[CONTRIBUTION FROM THE LABORATORIES OF THE UNIVERSITY OF MARYLAND]

The Reaction of Styrene Oxide with Methanol

BY WILKINS REEVE AND IVAN CHRISTOFFEL

The reactions of styrene oxide with various nucleophilic reagents have recently been studied by a number of investigators, but there appears to be no agreement as to whether a nucleophilic reagent can be expected to attack the α carbon or the terminal β carbon. The α position is reported to be the more reactive toward pyridine hydrochloride,[1] sodium phenoxide[2] and allyl alcohol in the presence of sodium alloxide.[3] An ether solution of magnesium iodide, and also hydrogen iodide dissolved in petroleum ether, add to styrene oxide with the iodine going to the α-position.[4,5] On the other hand, the β-position is reported to be the more reactive toward lithium aluminum hydride,[6] sodium malonic ester,[7] sodium methyl mercaptide,[8] most Grignard reagents[4,9] and various amines.[10] The acid catalyzed reaction of styrene oxide with alcohols is reported to give the secondary alcohol–primary ether isomer in the case of ethanol and butanol-1,[10] and to give a mixture of both isomers consisting predominantly of the secondary alcohol in the case of allyl alcohol.[3]

The reaction of styrene oxide with aliphatic alcohols was first studied by Emerson[10]; however, it was previously observed by Späth[11] that an alcoholic solution of sodium ethoxide reacted with 1-phenyl-2-chloroethanol to produce styrene oxide and a monoethyl ether of styrene glycol. The latter could have resulted from the reaction of the excess alcohol with the styrene oxide. This observation rendered invalid the structural proof advanced by Tiffeneau[12] and later by Emerson[10] in support of the alcohol ethers they synthesized from 1-phenyl-2-haloethanol. Kaelin[13] demonstrated the presence of 1-phenyl-2-methoxyethanol in the material obtained by the sodium methoxide catalyzed reaction of styrene oxide and methanol. He believed this material contained both isomers.

The object of this work was to reinvestigate the reaction of styrene oxide with a typical aliphatic alcohol such as methanol, and to determine the ratio of the isomers produced in the base and acid catalyzed reactions. The experimental approach

(1) King, Berst and Hayes, THIS JOURNAL, **71**, 3498 (1949).

(2) Guss, *ibid.*, **71**, 3460 (1949).

(3) Swern, Billen and Knight, *ibid.*, **71**, 1152 (1949).

(4) Golumbic and Cottle, *ibid.*, **61**, 996 (1939).

(5) Tiffeneau, *Ann. chim. phys.*, [8] **10**, 348 (1907).

(6) Trevoy and Brown, THIS JOURNAL, **71**, 1675 (1949).

(7) Russell and VanderWerf, *ibid.*, **69**, 11 (1947).

(8) Gilman and Fullhart, *ibid.*, **71**, 1478 (1949).

(9) Kharasch and Clapp, *J. Org. Chem.*, **3**, 355 (1938). These investigators found the site of reaction of phenylmagnesium bromide to depend on the order of addition of the reagents.

(10) Emerson, THIS JOURNAL, **67**, 516 (1945).

(11) Späth, *Monatsh.*, **36**, 7 (1915).

(12) Tiffeneau, *Compt. rend.*, **145**, 811 (1907).

(13) Kaelin, *Helv. Chim. Acta*, **30**, 2132 (1947).

Table I

Properties of the Monomethyl Ethers of Styrene Glycol

Materials	Composition I, %	Composition II, %	Viscosity at 25°, poises	Recryst. α-naphthylurethan, m. p., °C.[a]	Boiling points, °C. at 760 mm.	°C. at	Mm.	$n^{25}D$	d^{25}_4	OCH_3, % (th. 20.39)	Carbon, % (th. 71.02)	Hydrogen % (th. 7.95)
2-Phenyl-2-methoxyethanol from α-methoxyphenylacetic acid	100		0.154	119.5	236.9	134 79	30 ~2	1.5182	1.0612	20.31	71.07	8.16
1-Phenyl-2-methoxyethanol, from ω-methoxyacetophenone		100	.0863	105	242.3	137–138	30	1.5190	1.0617	20.30	71.10	8.00
Mixed isomers from base catalyzed reaction. Method A. (120 g.)	34	66	.105	...		70–75	2	1.5187		20.05	71.05	8.07
From distillation of above:												
Fraction 1a (5 g.)	78	22	.134	119.5	237.7	91	~3			20.07	71.04	8.08
Fraction 1b (26 g.)	45	55	.112		239.5	75	2			20.40	71.10	8.04
Fraction 2 (31 g.)	37	63	.170		240.2	75–77	2			20.08	71.15	8.15
Fraction 3 (30 g.)	11	89	.0920	104.5	241.3	77–79	2			20.41	71.00	8.06
Mixed isomers from base catalyzed reaction, Method B	25	75	.0998		241.1	72	1.5–2	1.5190		20.25	71.38	8.27
Mixed isomers from acid catalyzed reaction	90	10	.1437	119.5	236.3	93	4	1.5182		20.12	71.04	8.07

[a] The three derivatives of m. p. 119.5° gave no depression when mixed. A mixed m. p. of the two derivatives, m. p. 104.5–105°, gave no depression. Mixed m. p. of 104.5–105° derivatives with 119.5° derivatives was 89°.

has been to obtain each isomer in a pure state by independent syntheses, and to determine the composition of the mixed isomers, obtained from styrene oxide and methanol, by a comparison with these pure standards.

2-Phenyl-2-methoxyethanol (I) was prepared by the lithium aluminum hydride reduction of α-methoxyphenylacetic acid and also by the hydrogenation of the ethyl ester of this acid. The other isomer, 1-phenyl-2-methoxyethanol (II), was prepared by the hydrogenation of ω-methoxyacetophenone. The two pure isomers were found to have almost identical densities and indices of refraction, and to have boiling points differing by only five degrees at atmospheric pressure. The α-naphthylurethans were found to be suitable derivatives.

The problem of analyzing a mixture of these pure isomers was solved with the discovery that the primary alcohol (I) had almost twice the viscosity of the secondary alcohol (II), and a method of analyzing mixtures of the isomers was developed based on this difference in physical properties. In order to guard against the presence of third components causing erroneous conclusions to be drawn from the viscosity data, data were obtained only on samples distilling in the correct temperature range, and in addition each sample was analyzed for carbon, hydrogen, and methoxyl to insure that only the two isomers were present. Data on the viscosity of the pure isomers and their mixtures are given in Fig. 1.

The sulfuric acid catalyzed reaction of styrene oxide and methanol yielded a mixture of the isomeric methoxy alcohols consisting of 90% of the primary alcohol (I). When the reaction was catalyzed with sodium methoxide, a mixture was again obtained, but in this case it consisted of 66–75% of the secondary alcohol (II). One of the base catalyzed reactions was subjected to a careful fractional distillation and fractions of each isomer obtained which viscosity analysis showed were 78% isomer (I) and 89% isomer (II). From these fractions the α-naphthylurethans of the major constituent were easily isolated. Data on all of the mixtures and on the pure compounds are summarized in Table I.

The methoxy alcohols from both the acid and

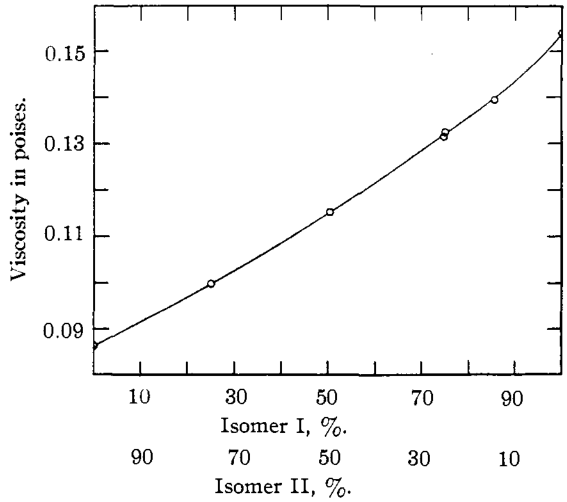

Fig. 1.—Viscosity of mixtures of 2-phenyl-2-methoxyethanol (I) and 1-phenyl-2-methoxyethanol (II).

base catalyzed reactions contained traces of carbonyl compounds as shown by a small precipitate when treated with a saturated aqueous solution of 2,4-dinitrophenylhydrazine in 2 *N* hydrochloric acid. In view of the analytical data and the size of the precipitates, the carbonyl contaminator must be present in only trace amounts. The pure synthetic isomers did not give a precipitate with this reagent.

Assuming methanol, ethanol and butanol-1 to react similarly with styrene oxide, the products obtained by Emerson[10] in his acid catalyzed reactions of ethanol and butanol-1 with styrene oxide must have predominantly the primary alcohol–secondary ether structure and not have the secondary alcohol–primary ether structures which he assigned. The products which he, Tiffeneau,[12] Späth[11] and Detoeuf[14] obtained from the 1-phenyl-2-haloethanols and metal alkoxides are undoubtedly mostly of the secondary alcohol–primary ether type, since these would predominate regardless of whether or not the epoxide was an intermediate in the reaction; however, it is doubtful if pure secondary alcohol–primary ether isomers can be obtained in this way.

The direction of addition of allyl alcohol to styrene oxide, as determined by Swern,[3] is the opposite of that which we have observed with methyl alcohol. Accordingly, the two tests used to chemically differentiate the primary and secondary monoalloxy ethers of styrene glycol were tried with the corresponding monomethyl ethers. 2-Phenyl-2-methoxyethanol (I) reacted more rapidly with benzoyl chloride than did the isomeric secondary alcohol. On the other hand, the primary alcohol isomer (I) reacted quite sluggishly with metallic sodium over a period of several days whereas the secondary alcohol isomer (II) dissolved the sodium within eight hours. This unexpected unreactivity of the primary alcohol is probably due to the fact that the sodium salt of the primary alcohol is insoluble and forms a protective coating over the sodium.

Experimental

All melting and boiling points are "corrected." The boiling points at 760 mm. in Table I were determined by suspending a calibrated Anschütz thermometer in a 2.5 × 18 cm. test-tube containing 2 to 3 ml. of the boiling material. Analyses are by Mrs. Mary Aldridge and Mr. Byron Baer of this laboratory. Refractive indices were determined with an Abbe refractometer. Densities were determined with a pycnometer having a volume of approximately 3 ml. and are believed to be accurate to within ±0.0003.

Materials.—Commercial styrene oxide was used without further purification, except where otherwise stated. Methanol was dried over calcium oxide.

Sodium Acid Salt of α-Methoxyphenylacetic Acid.—This new compound was prepared by a modification of Braun's method[15] for the methylation of mandelic acid by adding 609 g. (4 moles) of *dl*-mandelic acid to a hot solution made by dissolving 2120 g. (53 moles) of sodium hydroxide in 7 l. of water. The reaction was carried out in a 5 gal. can to minimize the effect of foaming during the methylation. After cooling to 45–50°, 2774 g. (22 moles) of distilled dimethyl sulfate was added over a period of one and one-half to two hours, the reaction temperature remaining unchanged. After cooling to room temperature, the precipitate (mixture of normal sodium salts of mandelic and α-methoxyphenylacetic acids and inorganic salts) was filtered (dry weight 500–600 g.). It was dissolved in 2.5 l. of hot distilled water and the sodium acid salt precipitated by adding concentrated hydrochloric acid to a *p*H of 3.1. The mixture was cooled to 20° and filtered. The weight was 220–265 g. after air drying. An additional 24–30 g. was obtained by adding 150 g. of sodium chloride to the filtrate. The combined materials were dissolved in 10 times their weight of boiling distilled water, filtered, cooled to 20° and the precipitate filtered. Additional sodium acid salt was recovered from the filtrate by adding a solution of sodium chloride, filtering, and recrystallizing from 10 times its weight of water. The combined precipitates weighed 240–295 g., yield 34–42%.

Anal. Calcd. for $C_{18}H_{19}O_6Na$: OCH_3, 17.52; neut. equiv., 354.3. Found: OCH_3, 17.47; neut. equiv., 352.

α-Methoxyphenylacetic acid was prepared from 354 g. (1 mole) of the sodium acid salt of α-methoxyphenylacetic acid by treating a hot aqueous solution (2 l.) of it alternately with a total of 42 ml. of concentrated hydrochloric acid and more of the sodium acid salt. The addition of a large excess of hydrochloric acid to the hot solution was avoided. The oily α-methoxyphenylacetic acid which separated was extracted three times with ether from the cooled solution to which 100 ml. more concentrated hydrochloric acid had been added, the ether extracts combined, washed once with a little water, dried, and the ethyl ether removed by distillation. The residual solid, m. p. 70.5–71°, weighed 282–320 g., yield 88–97%. The melting point was still 70.5–71°, in agreement with the reported value,[15] after recrystallizing 50 g. from 1500 ml. of petroleum ether (boiling range 90–100°).

2-Phenyl-2-methoxyethanol (I) was prepared by the lithium aluminum hydride reduction of α-methoxyphenylacetic acid according to the general procedure of Nystrom and Brown[16] for phenylacetic acid. The yield was 55%. The **α-naphthylurethan** was prepared in the usual way,[17] m. p. 119.5°, after five recrystallizations from petroleum ether (boiling range, 90–100°) and one recrystallization from a dilute ethanol–water solution in which activated carbon was employed. *Anal.* Calcd. for $C_{20}H_{19}NO_3$: C, 74.74; H, 5.96; N, 4.39; OCH_3, 9.65. Found: C, 74.67; H, 6.04; N, 4.51; OCH_3, 9.61.

Isomer I was also prepared by the copper chromite catalyzed hydrogenation of ethyl α-methoxyphenylacetate under the usual conditions for esters. The material contained small amounts of β-phenylethyl alcohol and in attempting to remove this by fractional distillation, some thermal decomposition of I occurred and the carbon analyses obtained were about 0.6% low.

ω-Methoxyacetophenone was prepared from methoxyacetonitrile and phenylmagnesium bromide.[18] The material was contaminated with diphenyl and phenol, but these were not removed until after hydrogenation to the methoxy alcohol. The **semicarbazone** was prepared, m. p. 126–127° in agreement with Dufraise and Chaux.[19]

1-Phenyl-2-methoxyethanol (II) was prepared by the hydrogenation of 50 g. of ω-methoxyacetophenone over 5 g. of copper chromite catalyst at 145° and 160 atm. starting pressure in absolute ethanol. The hydrogenation was repeated twice to insure complete reduction. Diphenyl and phenol were later found to be present as impurities. These were removed by dissolving the material in 75 times its weight of aqueous ethanol, the amount of ethanol being

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(14) Detoeuf, *Bull. soc. chim.*, [4] **31**, 176 (1922).

(15) Braun, Anton and Weissbach, *Ber.*, **63**, 2847 (1930).

(16) Nystrom and Brown, THIS JOURNAL, **69**, 2548 (1947).

(17) Shriner and Fuson, "The Systematic Identification of Organic Compounds," John Wiley and Sons, Inc., New York, N. Y., 2nd ed., 1940, p. 136.

(18) "Organic Syntheses," Vol. 21, John Wiley and Sons, Inc., New York, N. Y., 1941, p. 79.

(19) Dufraise and Chaux, *Bull. soc. chim.*, **39**, 443 (1926).

just sufficient to prevent the separation of the methoxy alcohol. The precipitated diphenyl was filtered off, the ethanol removed by distillation, and the material salted out by the use of the anhydrous potassium carbonate. It was then carefully distilled several times. The final distillation was through a 50-cm. glass helices-packed column. The over-all yield was 17 g. of pure material. The α-**naphthylurethan** was prepared in the usual way,[17] m. p. 105° after three recrystallizations from petroleum ether (boiling range 90–120°). *Anal.* Calcd. for $C_{20}H_{19}NO_3$: C, 74.74; H, 5.96; N, 4.39; OCH_3, 9.65. Found: C, 74.59; H, 6.04; N, 4.52; OCH_3, 9.81.

Acid-catalyzed Reaction of Styrene Oxide and Methanol.—This followed Emerson's procedure F.[10] Twenty-nine grams (0.9 mole) of methanol (dried over calcium oxide) and 0.2 ml. of concentrated sulfuric acid were heated to reflux and 72 g. (0.6 mole) of styrene oxide added over a 15-minute period. The mixture was refluxed for five hours, cooled, neutralized with sodium bicarbonate solution, dried over potassium carbonate and distilled: 38 g., b. p. 83–84° (2 mm.), yield 42%, which was redistilled through a modified Widmer column, b. p. 93° (4 mm.). An additional 25 g. of material was obtained, b. p. 120–170° (2 mm.), presumed to be a diphenyldioxane.[10]

Base Catalyzed Reaction of Styrene Oxide and Methanol.—This was carried out (Method A) by dissolving 0.5 g. of sodium in 120 ml. (3 moles) of dry methanol, and slowly adding 120 g. (1 mole) of redistilled styrene oxide to the refluxing solution over a period of one and one-half hours. The mixture was refluxed for an additional six hours, the excess methanol removed by distillation under reduced pressure, and the residue washed with water. The water washing was extracted with ether, and the combined residue and ether extracts dried over anhydrous magnesium sulfate and distilled. There was obtained 120 g., b. p. 70–75° (2 mm.), yield 79% and 19 g. polymeric by-product. The 120 g. fraction was refractionated through a 50-cm. glass helices packed column to give the series of fractions described in Table I.

Method B involved the use of 60 ml. (1.5 moles) of methanol, 5 g. of sodium, and 60 g. (0.5 mole) of styrene oxide. This represents a twenty-fold increase in the concentration of the base. The procedure was the same as in Method A, except the addition of the styrene oxide was at 0°, the mixture was then stirred 3 hours at 0°, and finally allowed to warm up to room temperature. There was obtained 52 g. (68% yield), b. p. 72° (1.5–2 mm.), of a mixture of isomers I and II as given in Table I, and 12 g. of high boiling material.

Viscosity determinations were carried out with 3-ml. samples in the standard Ostwald viscometer in a water-bath maintained at 25 ± 0.1°. Freshly distilled β-phenylethyl alcohol, b. p. 219–220 (760 mm.), n^{17}_{D} 1.5332, reported to have a viscosity of 0.07580 poises at 25°[20] and an $n^{16.8}_{\mathrm{D}}$ 1.5337,[21] was used to standardize the viscometer; values of 18 min., 41 sec. and 18 min., 38 sec. were obtained. Accordingly, the averaged observed times of the samples examined were multiplied by the factor (0.07580)(1.0614)/(18.66)(1.023) = 0.00422 to obtain the viscosity in poises as reported in Table I and Fig. 1.

When water was used as a standard, times of 1 min., 31 sec. and 1 min., 31 sec. were obtained. This gives a factor of 0.00628. It is well known the standard chosen to calibrate a viscometer should have approximately the same viscosity as the samples being measured, so this factor was not used.

Degree of Reaction with Benzoyl Chloride.—The benzoylation procedure of Kadesch[22] was employed, except dimethylaniline was substituted for diethylaniline. The extent of reaction with pure isomer I was found to be 45 and 55%. With pure isomer II, values of 13.7 and 15.6% were obtained.

Rate of Reaction with Metallic Sodium.—The procedure of Swern[3] was followed. The acid-catalyzed fraction (90% I, 10% II) required three days, even though the surface of the sodium was cleaned and enlarged by occasionally mashing it with a glass rod. Fraction 3 (10% I, 90% II) dissolved the sodium within eight hours. The above tests were repeated on one-tenth the above scale with the pure isomers and similar results obtained. The secondary alcohol isomer (II) dissolved the sodium within three hours at 35° whereas the primary alcohol isomer (I) required two days at 35°.

Summary

Styrene oxide reacts with methanol in the presence of sulfuric acid to give a mixture of the isomeric methyl ethers of styrene glycol consisting of 90% of the primary alcohol–secondary ether, 2-phenyl-2-methoyxethanol, and 10% of the other isomer.

Styrene oxide reacts with methanol in the presence of sodium methoxide to give a mixture of the isomers consisting of 66–75% of the secondary alcohol–primary ether, 1-phenyl-2-methoxyethanol, and 34–25% of the primary alcohol–secondary ether.

2-Phenyl-2-methoxyethanol has been obtained in a pure state by the reduction of α-methoxyphenylacetic acid.

1-Phenyl-2-methoxyethanol has been obtained in a pure state by the hydrogenation of ω-methoxyacetophenone.

The primary alcohol isomer has approximately twice the viscosity of the secondary alcohol isomer.

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[20] Dunstan, Hilditch and Thole, *J. Chem. Soc.*, **103**, 133 (1913).

[21] Cotton and Mouton, *Ann. chim. phys.*, [8] **28**, 214 (1913).

[22] Kadesch, THIS JOURNAL, **68**, 41 (1946).