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Styrene Derivatives. IX. 2-Benzyl-2-phenyl-3-aminomethyl-trimethylene Oxides and Related Compounds1)

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3-Chloromethyl-4-chloro-1, 2-diphenylbutan-2-ol was obtained by a Grignard reaction of 2-benzoyl-1, 3-dichloropropane using benzyl chloride, which was turned into 2-benzyl-2-phenyl-3-chloromethyl-trimethylene oxide by the alkali dehydrochlorination. Heating this oxide with an excess of piperidine at 170°C for 22 hr. gave 2-benzyl-2-phenyl-3-piperidinomethyl-trimethylene oxide and a small amount of 1, 2-diphenyl-3-piperidinomethyl–2, 4-butanediol. The same procedures with morpholine gave 2-benzyl-2-phenyl-3-morpholinomethyl-trimethylene oxide; with ethanolic dimethyl amine, however, afforded only 1, 2-diphenyl-3-dimethylamino-methyl-2, 4-butanediol.

During the synthetic studies of styrene derivatives which have been developed in our former laboratory,2) 2-benzoyl-1, 3-dichloropropane (I) was previously prepared from acetophenone via the 5-benzoyl-1, 3-dioxane obtained by the acidic-aldol condensation of acetophenone with formaldehyde.3) The present paper will deal with the syntheses of 2-benzyl-2-phenyl-3-aminomethyl-trimethylene oxides and the hydrated aminodiol compounds, using this 2-benzoyl-1, 3-dichloropropane as a synthetic intermediate. We expect to be able thus to determine the physiological activities of these amino compounds and the availabilities in the field of synthetic drugs, and also some information about the reaction course.

The reaction of I with a Grignard solution prepared from benzyl chloride easily gave 3-chloromethyl-4-chloro-1, 2-diphenylbutan-2-ol (II). The dehydrochlorination of II with an excess of ethanolic potassium hydroxide under reflux preferentially afforded III as the product. The compound III did not decolorize permanganate, and its infrared spectrum shows a strong band at 966 cm^{-1} assignable to trimethylene oxide4) and has neither the characteristic peak of hydroxyl nor of the vinylidene group. Therefore, the structure of III must be 2-benzyl-2-phenyl-3-chloromethyl-trimethylene oxide.

It was found that the remaining chlorine atom in the compound III was too stable to react with either such an alkali as above or the amines used in this report under such mild conditions as below 100°C, but when it was heated at 160—170°C over 20 hr. it could be substituted with such amines to give the attempted amino compounds, besides 1, 2-diphenyl-3-aminomethyl-2, 4-butanediols. The VI amines were also confirmed to be trimethylene oxide compounds; their infrared spectra clearly indicate the characteristic band of the trimethylene oxide ring in the region near 980 cm^{-1}.

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1) Styrene Derivatives, Paper VIII: A. Terada, *J. Chem. Soc. Japan, Pure Chem. Sect. (Nippon Kagaku Zasshi)*, **81**, 1465 (1960).

2) Government Industrial Research Institute, Osaka, Oyodo-ku, Osaka.

3) A. Terada, *J. Chem. Soc. Japan, Pure Chem. Sect. (Nippon Kagaku Zasshi)*, **81**, 612 (1960).

4) G. M. Barrow and S. Searles, *J. Am. Chem. Soc.*, **75**, 1175 (1953).

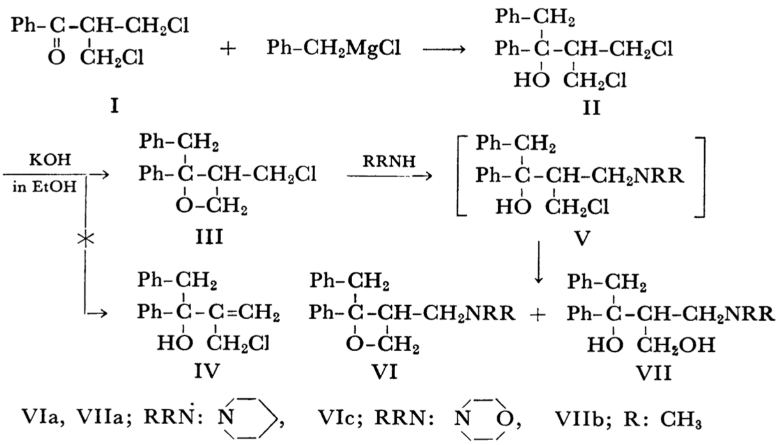

Fig. 1

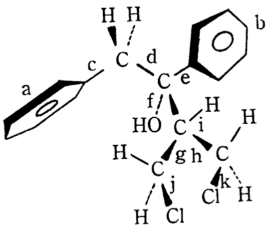

Fig. 2

The conformation of II may be sketched stereochemically as in Fig. 2 using a Stuart-type molecular model in which the ring a is nearly horizontal and the ring b almost vertical. The observation of the model also strongly suggests that the free rotations about the bonds of c, d, e, f, g and h are virtually impossible, and that in view of their preferred conformations, both the chlorine atoms may jut together to this side. The repulsion between two chlorine atoms should, therefore, be so large that it is obvious that one of the chlorines is excessively reactive. However, both the chlorine atoms can not be placed in the *trans* conformation to the *i*-hydrogen, because there are serious restrictions of free rotation about the bonds g and h as has been mentioned above. The chlorine atom will preferentially react with the hydroxyl group of the back side, and the system will proceed to a ring closure to give the trimethylene oxide (III) by an S_N2 reaction rather than to a formation of the vinylidene compound (IV) by a *trans* E2 reaction.

It is believed that the bimolecular substitution of the remaining chlorine atom in the compound III with amine will be hindered greatly by the crowded back and that, therefore, it will be less reactive. We, therefore, assume that the compound III reacts with such amines to form an intermediate V, aminated chlorohydrin, which is a normal addition product of trimethylene-oxide ring opening effected exclusively by steric reasons, and that it immediately turns into the principal product, VI, as is shown in Fig. 1. Support for this conclusion can be obtained by the following fact. Searles and Gregory have reported that, while trimethylene oxide reacts with amines less readily at moderate temperatures, when the temperature rises to 150°C it undergoes ring opening to give the corresponding aminopropanols in good yields.5)

Experimental

3-Chloromethyl-4-chloro-1,2-diphenylbutan-2-ol (II).—An ethereal solution of benzyl magnesium chloride was prepared in the usual manner with 50 ml. of anhydrous ether, 6.1 g. of magnesium foils, and 28.2 g. (0.22 mol.) of benzyl chloride in 50 ml. of anhydrous ether. A solution of 43.4 g. (0.2 mol.) of 2-benzoyl-1,3-dichloropropane3) in 85 ml. of anhydrous ether was added, drop by drop, into the Grignard reagent under vigorous stirring and ice cooling over a period of 25 min. The reaction mixture became cloudy in the early stages of the reaction, and then it became clear. After it had settled overnight at room temperature, the mixture was treated with ice water, made acidic with hydrochloric acid, and taken up in benzene. The benzene solution was washed with water, a saturated sodium bicarbonate solution, and water again, and then dried over anhydrous sodium sulfate. Upon the removal of the solvent under reduced pressure and cooling, 29.8 g. (48.2%) of crude crystals were yielded. Recrystallization from benzene - petroleum benzine gave an analytical sample of II melting at 76—77.5°C.

Found: C, 65.89; H, 6.03. Calcd. for $C_{17}H_{18}Cl_2O$: C, 66.03; H, 5.87%.

ν_{max}^{Nujol} 3704 (OH); 3035, 1603, 1504 (phenyl); 1344, 1151 (tertiary alcohol); 761, 746, 692 cm^{-1} (monosubstituted benzene).6)

2-Benzyl-2-phenyl-3-chloromethyl-trimethylene Oxide (III).—A sample of 15.2 g. (0.05 mol.) of II

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5) S. Searles and V. P. Gregory, *J. Am. Chem. Soc.*, **76**, 2789 (1954).

6) The infrared spectra were taken on a Perkin-Elmer spectrophotometer, Model 21 (NaCl).

was refluxed with 2.8 g. (0.05 mol.) of potassium hydroxide in 10 ml. of ethanol. The reaction was exothermic, and potassium chloride crystals were precipitated immediately. After another hour's refluxing, the reaction mixture was poured into water and taken up in benzene. The benzene layer was washed with water until the washings were neutral, and then dried over anhydrous sodium sulfate. The remaining oil, upon the removal of the solvent, was induced to crystallize by trituration with petroleum benzine under cooling. The isolated crude crystals (5.33 g.; 39%) were recrystallized from petroleum benzene to give an analytical sample of III, white crystals, m. p. 83.5—84.5°C.

The use of a two-molar equivalent of potassium hydroxide against III gave a yield nearly twice as good.

Found: C, 74.71; H, 6.44; Cl, 12.92. Calcd. for $C_{17}H_{17}ClO$: C, 74.85; H, 6.28; Cl, 13.00%.

ν_{max}^{Nujol} 3021, 1600, 1495 (phenyl); 1155, 1145, 1029, 774, 750, 711, 702 (mono-substituted benzene); 966 cm^{-1} (trimethylene oxide).[4]

The Reaction of III with Piperidine.—A mixture of 2.20 g. (8.07 mmol.) of III and 5.50 g. of piperidine (b. p. 106°C) in a sealed tube was heated at 170°C for 22 hr. The contents were then evaporated under reduced pressure, and the remaining oil, after being alkalized with a dilute sodium hydroxide solution, was repeatedly extracted with benzene. The benzene solution was washed with water and dried over anhydrous sodium sulfate. After the removal of the solvent, the oily product was combined with 1.5 ml. of concentrated hydrochloric acid to give a white precipitate of the hydrochloride. Crystallization from water yielded 1.65 g. (55.8%) of crystals, m. p. 197—198°C. An analytical sample was obtained from another recrystallization, m. p. 200—201°C, 2-benzyl-2-phenyl-3-piperidinomethyl-trimethylene oxide hydrochloride · a half hydrate (VIa·HCl·1/2 H_2O).

Found: C, 72.01; H, 8.10; N, 4.13; H_2O, 3.10. Calcd. for $C_{22}H_{27}NO\cdot HCl\cdot 1/2H_2O$: C, 72.01; H, 7.97; N, 3.82; H_2O, 2.45%.

ν_{max}^{Nujol} 3635, 3289, 1621 (H_2O); 2710—2410 (tertiary amine hydrochloride); 979 (trimethylene oxide); 767, 754, 699, 695 cm^{-1} (mono-substituted benzene).

The anhydrous hydrochloride was obtained by drying it at 100°C under a vacuum until a constant weight was obtained, but the melting point remained unchanged. The infrared spectrum of the dried hydrochloride showed no absorption bands characteristic of the water of crystallization in the region of 3635, 3289 and 1621 cm^{-1}.

Free Amine (VIa).—This was obtained as usual, m. p. 49.5—50.5°C. It may be hydrated, because the following infrared spectral data show a weak absorption peak of the hydroxyl group. When the mother liquor, from which VIa·HCl had been effectively removed, was concentrated, a small amount of white crystals remained. Recrystallization from water gave an analytical sample of 1, 2-diphenyl-3-piperidinomethyl-2, 4-butanediol hydrochloride (VIIa·HCl), m. p. 219—220°C.

Found: C, 70.28; H, 8.20; N, 3.92. Calcd. for $C_{22}H_{29}NO_2\cdot HCl$: C, 70.29; H, 8.04; N, 3.73%.

ν_{max}^{Nujol} 3413, 3215 (OH); 2732—2410 (tertiary amine hydrochloride); 3030, 1605, 1502 (phenyl); 1136 (C–O, tertiary alcohol); 1064 (C–O, primary alcohol); 771, 755, 702, 698 cm^{-1} (mono-substituted benzene).

The Reaction of III with Dimethyl Amine in Ethanol.—A sample of 1.37 g. (5 mmol.) of III was dissolved in 7.0 g. of 33% ethanolic dimethyl amine and heated in a sealed tube at 170°C for 33 hr. After working-up as usual, the oily product was repeatedly extracted with dilute hydrochloric acid under heating. The combined extract was concentrated under diminished pressure, and the remaining crystals were washed with acetone to give 0.77 g. (45.9%) of 1, 2-diphenyl-3-dimethylaminomethyl-2, 4-butanediol hydrochloride (VIIb·HCl) as white crystals, m. p. 213—214°C.

Found: C, 66.74, 66.90; H, 7.98, 7.97; N, 4.14, 4.03. Calcd. for $C_{19}H_{25}NO_2\cdot HCl\cdot 1/3H_2O$: C, 66.74; H, 7.27; N, 4.10%.

ν_{max}^{Nujol} 3279 (OH); 3049, 1603, 1493 (phenyl); 2801 ($N\text{-}CH_3$); 1377 (methyl); 1060 (C–O, primary alcohol); 765, 744, 703, 699 cm^{-1} (mono-substituted benzene).

Free Amine (VIIb).—This was obtained as usual, m. p. 135—136°C (from benzene).

Found: C, 75.96; H, 8.38. Calcd. for $C_{19}H_{25}NO_2$: C, 76.22; H, 8.42%.

ν_{max}^{Nujol} 3378 (OH); 3012, 1600, 1493 (phenyl); 2793 ($N\text{-}CH_3$); 1376 (methyl); 1059 (C–O, primary alcohol); 768, 747, 699, 696 cm^{-1} (mono-substituted benzene).

The Reaction of III with Morpholine.—A mixture of 2.725 g. (10 mmol.) of III and 8.70 g. (100 mmol.) of morpholine (b. p. 128°C) was heated in a sealed glass tube at 170°C for 28 hr. After working-up as usual and the subsequent hydrochlorination of the product, crystallization from *n*-butanol gave 1.58 g. (47.2%) of 2-benzyl-2-phenyl-3-morpholinomethyl-trimethylene oxide hydrochloride (VIc·HCl), m. p. 197.5—202°C. Recrystallization from water raised the melting point to 203—204.5°C, white crystals.

Found: C, 69.94; H, 7.57; N, 3.99. Calcd. for $C_{21}H_{25}NO_2\cdot HCl$: C, 70.08; H, 7.03; N, 3.89%.

ν_{max}^{KBr} 3360, 2710, 2690, 2480 (tertiary amine hydrochloride); 1960, 1895, 1815, 1758, 780, 764, 748, 700 (mono-substituted benzene); 1600, 1580, 1490 (phenyl); 980 cm^{-1} (trimethylene oxide).

Free Amine (VIc).—This was obtained by the same procedure in a 48.2% yield, and also from the alkali treatment of the above hydrochloride, white needles (VIc·1/3H_2O), m. p. 67—68°C (from petroleum benzine).

Found: N, 4.37; H_2O, 1.87. Calcd. for $C_{21}H_{25}NO_2\cdot 1/3H_2O$: N, 4.25; H_2O, 1.82%.

ν_{max}^{KBr} 3470, 1631 (water of crystallization); 3080, 3040, 1610, 1500 (phenyl); 1958, 1885, 1818, 1760, 773, 756, 705 (mono-substituted benzene); 980 cm^{-1} (trimethylene oxide).

The anhydrous VIc was obtained as usual; it showed no absorption bands of the infrared spectrum characteristic of the water of crystallization at such regions as 3470 and 1631 in the above hydrated sample.

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