Experimental Section[5]

2-Isopropyl-5,5-bis(hydroxymethyl)-1,3-dioxane (2).—Isobutyraldehyde (26.5 g, 0.38 mol) and 23 ml of concentrated hydrochloric acid were added to a stirred solution of 50 g (0.37 mol) of pentaerythritol in 2.9 l. of water. After the mixture had been stirred for 24 hr at room temperature, insoluble solids were removed and the pH was adjusted to 8 with solid sodium carbonate. Water was evaporated and the solid residue was extracted with 800 ml of boiling *p*-xylene. After filtration, the extract stood overnight at 5°. The product weighed 25.3 g (36.4%), mp 97–99°.

Anal. Calcd for $C_9H_{18}O_4$: C, 56.8; H, 9.5; mol wt, 190.2. Found: C, 56.7; H, 9.4; mol wt, 188.

3,3-Bis(hydroxymethyl)-1,5-dioxaspiro[5.5]undecane (3).—The compound was prepared in 3.5% yield by the procedure of Issidroides and Gulen,[5] mp 125–127°.

Anal. Calcd for $C_{11}H_{20}O_4$: C, 61.1; H, 9.3; mol wt, 216.2. Found: C, 61.1; H, 9.1; mol wt, 216.

2-Phenyl-5-carboxy-5-hydroxymethyl-1,3-dioxane (1a).—Dioxane **1a** was prepared according to a procedure published by Sulzbacher, *et al.*,[6] in 67.2% yield, mp 176–178°.

Anal. Calcd for $C_{12}H_{14}O_5$: C, 60.5; H, 6.0; mol wt, 238.2. Found: C, 60.5; H, 6.1; mol wt, 229.

2-Isopropyl-5-carboxy-5-hydroxymethyl-1,3-dioxane (2a).—The dioxane was prepared in 29% yield, mp 149–151°.

Anal. Calcd for $C_9H_{16}O_5$: C, 52.9; H, 7.9; mol wt, 204. Found: C, 52.9; H, 7.9; mol wt, 226.

3-Carboxy-3-hydroxymethyl-1,5-dioxaspiro[5.5]undecane (3a).—Compound **3a** was prepared in 47.3% yield, mp 132–134°.

Anal. Calcd for $C_{11}H_{18}O_5$: C, 57.4; H, 7.9; mol wt, 230.2. Found: C, 57.8; H, 7.9; mol wt, 247.

2,2-Dimethyl-5-carboxy-5-hydroxymethyl-1,3-dioxane (4a).—Compound **4a** was prepared in 79% yield with a 20:1 molar ratio of ketone to acid, mp 128–130°.

Anal. Calcd for $C_8H_{14}O_5$: C, 50.5; H, 7.4; mol wt, 190.2. Found: C, 50.5; H, 7.5; mol wt, 185.

Preparation of Cells.—Growth of the parent strain was carried out on a medium containing 10.0 g of pentaerythritol, 2.0 g of acetic acid, 10 g of ammonium sulfate, 1.0 g of dipotassium hydrogen phosphate, 1.0 g of yeast extract, and 10 ml of mineral salts solution in 1 l. of distilled water adjusted to pH 7 with potassium hydroxide prior to sterilization.

The medium used for growth of the mutant strain has been reported.[1]

Flask culturing was carried out at 30° in 2.8-l. Fernbach flasks fitted with gauze closures. The inoculum was prepared in 25-ml erlenmeyer flasks fitted with Morton closures. The flasks were inoculated under sterile conditions from slants of either the parent strain[7] or the mutant strain (ATCC No. 21,245) and shaken on a rotary shaker at 400 rpm for 72 hr. Fernbach flasks were shaken at 150 rpm for 72 hr, after addition of a 5% (v/v) inoculum. Cells were harvested by centrifugation with a Sorvall refrigerated centrifuge operated at 9000 rpm for 20 min at 5°, freeze-dried in 0.4% potassium phosphate buffer, and stored at 5°.

Analysis of Oxidation Mixtures.—Acetals and ketals were estimated as the trimethylsilyl derivatives by gas–liquid chromatography.[1] Trimethylsilyl derivatives were prepared directly from freeze-dried samples of the oxidation mixtures. Standard curves were prepared with the chemically synthesized compounds using *n*-octadecane as the internal standard, with the exception of compounds **3** and **3a**, in which case *n*-dodecane was used. The accuracy of the estimation was 10%.

Biooxidation Reactions.—The oxidations were performed in 125-ml erlenmeyer flasks fitted with Morton closures. Cells (200 mg) and compound (225 mg) were suspended in 25 ml of nonsterile phosphate buffer. The mixtures were incubated at 30° on a shaker operated at 400 rpm. One-milliliter samples were removed at 24-hr intervals over a period of 7 days and analyzed.

Yield of product was reported based on the highest concentration observed during the incubation.

Product Identification.—Oxidation products were identified by comparison of the mass spectra of trimethylsilylated products isolated by gas–liquid chromatography with those of trimethylsilylated authentic samples (Table I).

Isolation of 2a.—Compound **2a** was prepared by a 20-fold scale-up of the biooxidation procedure. The cells were removed by centrifugation at 9000 rpm for 20 min at 5°. Ion exchange of the clarified solution was carried out on a column of Dowex 1 × 8 resin (100 ml in formate form). Elution was made with 4 *N* formic acid. Fractions containing pure product were freeze-dried. The product weighed 0.84 g (15.5%), mp 154–156°. A mixture melting point with an authentic sample was not depressed.

Registry No.—**1**, 2425-41-4; **1a**, 37951-01-2; **2**, 37951-03-4; **2a**, 37951-04-5; **3**, 714-88-5; **3a**, 38165-52-5; **4**, 770-74-1; **4a**, 16837-15-3; isobutyraldehyde, 78-84-2; pentaerythritol, 115-77-5.

Acknowledgment.—We wish to thank Dr. C. T. Goodhue for helpful advice, Mr. H. A. Risley for several samples of mutant cells, Mr. D. P. Maier for interpretation of the mass spectra, and Mr. R. E. Sceusa for technical assistance.

(5) Melting points are uncorrected. Molecular weights were obtained in acetone by the ebulliometric method. All evaporations were carried out under reduced pressure. The drying agent was sodium sulfate. Compounds **1** and **4** were prepared by published procedures [C. H. Issidroides and R. Gulen in "Organic Syntheses," Collect. Vol. IV, Wiley, New York, N. Y., 1963, p 679; L. Orther and G. Freyss, *Justus Liebigs Ann. Chem.*, **484**, 131 (1930)]. Gas chromatography was carried out with an F & M Model 810 gas chromatograph equipped with a thermal conductivity detector. The column was stainless steel 6 ft × 0.125 in. o.d. packed with SE-30 on Chromosorb W. A 30°/min column temperature rise from 100 to 300° was employed. Mass spectra were determined on either a Hitachi Perkin-Elmer RMS-4 or a C. E. C. 21-110B mass spectrometer.

(6) M. Sulzbacher, E. Bergman, and E. R. Pariser, *J. Amer. Chem. Soc.*, **70**, 2828 (1948); dioxanes **2a**, **3a**, and **4a** were also prepared by this method.

(7) This strain is maintained by Dr. C. T. Goodhue, Research Laboratories at Kodak Park Division of Eastman Kodak Co., Rochester, N. Y. 14650.

A Regiospecific Synthesis of 4-Chloroalkylbenzenes

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Although 4-chloro-1,2-dimethylbenzene (**1**) has been prepared in several different ways, each route has disadvantages as a practical synthetic method. Direct chlorination in the presence of Lewis acids results in formation of approximately equal amounts of the 3- and 4-chloro isomers.[1,2] These have been separated only by sulfonation, formation and fractional crystallization of the barium salts of the sulfonic acids, conversion of the barium salts to the sodium salts, and then desulfonation.[1] A multistep synthesis terminating in a Sandmeyer reaction of 3,4-dimethylbenzenediazonium chloride produces pure **1**,[3] but the yields are poor since nitration of *o*-xylene in the first step gives more 3- than 4-nitro-1,2-dimethylbenzene.[4,5]

Similar difficulties occur in the synthesis of other 4-haloalkylbenzenes, although separation of isomers is often simpler than in the case of **1**.

This paper reports a regiospecific synthesis of 4-

(1) A. Krüger, *Chem. Ber.*, **18**, 1755 (1885).

(2) A. Claus and O. Bayer, *Justus Liebigs Ann. Chem.*, **274**, 305 (1893).

(3) D. R. Lyon, F. G. Mann, and G. H. Cookson, *J. Chem. Soc.*, 662 (1947).

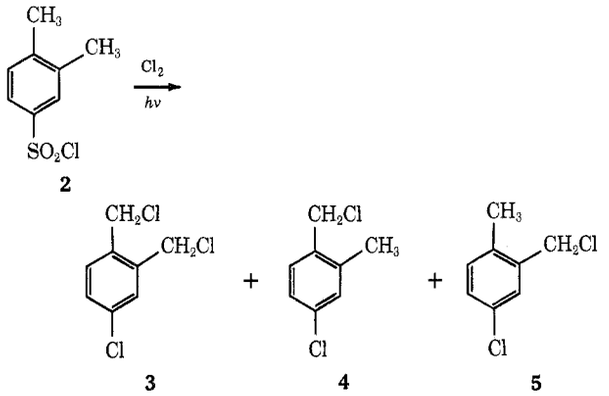
(4) A. W. Crossley and N. Renouf, *ibid.*, 202 (1909).

(5) Formation of **1** by reaction of 3,4-dimethylbenzenesulfonic acid with cuprous chloride has been reported: P. S. Varma, N. B. Parekh, and V. K. Subramanium, *J. Indian Chem. Soc.*, **16**, 460 (1939). I have been unable to reproduce this work.

chloro-1,2-dimethylbenzene and of 4-chlorotoluene. This method seems likely to be of general utility in the synthesis of 4-chloroalkylbenzenes.

It has been reported that chlorosulfonation of *o*-xylene gives 4-chlorosulfonyl-1,2-dimethylbenzene, with no mention of the 3 isomer being formed.[6] This reaction seemed a likely starting point for the specific formation of **1**, since conversion of aromatic chlorosulfonyl groups to chlorides has previously been reported.[7] Chlorosulfonation of *o*-xylene did indeed give 4-chlorosulfonyl-1,2-dimethylbenzene (**2**) as the major product, but nmr analysis indicated the presence of *ca.* 8–9% of a second isomer, presumably 3-chlorosulfonyl-1,2-dimethylbenzene. Recrystallization from ether gave pure **2** (mp 52–53°) in approximately 55% recovery from the crude sulfonation product.

Photochlorination of **2** was carried out until vpc analysis showed that less than 3% of the original sulfonyl chloride remained unreacted. Work-up of the reaction mixture gave a lachrymatory brown oil, whose ir spectrum showed the essential absence of sulfonyl peaks. The nmr spectrum similarly showed that the chlorosulfonyl group had been displaced by chlorine, but showed that, not unexpectedly, the methyl groups had also been chlorinated. The nmr spectrum of the crude product showed a strong singlet at δ 4.7, attributed to the methylene group of a benzyl choride, as well as peaks at δ 2.25 and 2.4 (in the area ratio 3:2) attributed to unreacted aromatic methyl groups. No signals appeared between δ 6 and 7, indicating the absence of any benzal chlorides. The area of the methylene signal was 2.6 times that of the combined methyl signals. If the assumption is made that no dimethyl compound remains in the mixture (an assumption supported by vpc analysis), and if the presence of small amounts of unreacted sulfonyl chloride is neglected, the spectrum indicates the photochlorination products to consist of 60% of **3** and 40% of a mixture of **4** and **5**.



Reduction of the crude chlorination product with zinc and hydrochloric acid gave (after distillation) pure **1** in overall 68% yield from **2**.

Repetition of the chlorination and reduction steps with the crude product of chlorosulfonation of *o*-xylene gave a product whose vpc, on several different columns, showed a single peak with a retention time identical with that of **1**. Its ir and nmr spectra, however, indicated that it contained about 8% of a second component, presumably 3-chloro-1,2-dimethylbenzene.

A similar sequence of chlorination and reduction steps (using iron in hydrochloric acid as the reducing agent) gave a 61% yield of *p*-chlorotoluene starting from *p*-toluenesulfonyl chloride.

While the goal of finding an essentially regiospecific path to 4-chloroalkylbenzenes had been accomplished, the overall yield of pure **1** from *o*-xylene was disappointing, owing to difficulties in recrystallizing the low-melting **2**. To overcome this difficulty, the crude product from chlorosulfonation of *o*-xylene was converted to bis(3,4-dimethylphenyl) sulfone.[8] The high-melting sulfone crystallized from the reaction mixture in high yield. Chlorination and reduction of the sulfone proceeded in essentially the same manner as did the reactions of the sulfonyl chloride to give **1** in an overall yield of 58% from *o*-xylene. Thus, despite the necessity for an extra step in the overall sequence, preparation of **1** *via* the sulfone seems the method of choice.

Experimental Section

Preparation of 3,4-Dimethylbenzenesulfonyl Chloride (2).—*o*-Xylene (20.0 g, 0.188 mol) in 200 ml of chloroform was cooled in an ice bath and stirred while chlorosulfonic acid (60 g, 0.51 mol) was added drop by drop. The solution was stirred for 1 hr at room temperature, and then for 1 hr at 50°. It was then cooled and poured onto ice. The chloroform layer was washed with water, dried over magnesium sulfate, and evaporated to give 40.0 g of pale yellow oil, which crystallized on standing in the cold to give an oily solid, mp 41–48°. Three recrystallizations from ether gave 21.1 g (0.103 mol, 55%) of 3,4-dimethylbenzenesulfonyl chloride, mp 52–53° (reported[8] mp 51–52°).

Preparation of Bis(3,4-dimethylphenyl) Sulfone.—A solution of crude 3,4-dimethylbenzenesulfonyl chloride (20.0 g, 0.098 mol) in *o*-xylene (10.4 g, 0.098 mol) was stirred at room temperature. Aluminum chloride (anhydrous) was added slowly, until the mixture became too viscous to stir. Water was added cautiously, and the mixture was then extracted with chloroform. The organic layer was washed with water and then with sodium bicarbonate solution and dried over magnesium sulfate. Evaporation of the solvent gave 26.1 g of pale yellow solid. Recrystallization from ethanol gave 22.3 g of bis(3,4-dimethylphenyl) sulfone (0.081 mol, 82%), mp 169–171° (reported[9] mp 162°).

Preparation of 4-Chloro-1,2-dimethylbenzene (1). A.—A stream of chlorine was passed through a solution of 3,4-dimethylbenzenesulfonyl chloride (10.0 g, 0.0487 mol) in 100 ml of chloroform. The solution was mechanically stirred and illuminated by a 150-W bulb at a distance of 2 in. At intervals, the chlorine stream was stopped and a sample of the solution was analyzed by vpc on a 6 ft, 3% SE-30 on Chromosorb W column at 185°. When the peak for 3,4-dimethylbenzenesulfonyl chloride (8.0 min) had essentially disappeared (2.5 hr) the reaction mixture was poured into sodium bisulfite solution, and the organic layer was washed with water and dried over magnesium sulfate. Evaporation of the solvent gave 9.3 g of a lachrymatory brown oil, which was dissolved in 25 ml of ethanol, and poured into 100 ml of concentrated hydrochloric acid which was rapidly stirred. Zinc dust (30.0 g, 0.46 g-atom) was added slowly to the mixture, with the evolution of much gas and an appreciable exotherm. The mixture was stirred for 1 hr after completion of the addition of the zinc, and was then extracted with chloroform. The organic layer was washed with sodium bicarbonate solution and with water and dried over magnesium sulfate. Evaporation of the solvent left 6.2 g of brown fluid, which was distilled under vacuum to give 4.65 g (0.033 mol, 68%), of 4-chloro-1,2-dimethylbenzene as a colorless liquid, bp 131–134° (25 mm).

B.—Chlorine gas was bubbled through a solution of bis(3,4-dimethylphenyl) sulfone (10.0 g, 0.0365 mol) in 200 ml of chloroform as described in part A. The course of the reaction was followed by ir spectroscopy. Introduction of chlorine was halted and the reaction was worked up as described above when the

(6) J. H. Uhlenbroek and M. Slagt, *Recl. Trav. Chim. Pays-Bas*, **80**, 1057 (1961).

(7) B. Miller and C. Walling, *J. Amer. Chem. Soc.*, **79**, 4187 (1957).

(8) O. Jacobsen, *Chem. Ber.*, **10**, 1009 (1877).

(9) H. Drews, S. Meyerson, and E. K. Fields, *J. Amer. Chem. Soc.*, **88**, 3871 (1961).

peak at 1090 cm^{-1} had essentially disappeared. The brown oil (13.2 g) obtained from the reaction was reduced as described above to give (after distillation) 7.28 g (0.052 mol, 71%) of 1.

Preparation of 4-Chlorotoluene.—*p*-Toluenesulfonyl chloride (15.0 g, 0.079 mol) was dissolved in 100 ml of chloroform, and the solution was stirred mechanically and irradiated by a 150-W incandescent bulb. Chlorine gas was passed through the solution until vpc analysis on a 6 ft, 3% SE-30 on Chromosorb W column showed that the *p*-toluenesulfonyl chloride was essentially completely reacted. The chlorine flow was stopped and the reaction mixture was worked up as described for the preparation of 1, to give 14.0 g of dark oil. The oil was suspended in 100 ml of rapidly stirred concentrated hydrochloric acid. Iron powder (7.0 g, 0.125 g-atom) was added slowly. The reaction mixture was stirred for 2 hr, filtered, and extracted with methylene chloride. The extract was washed with water and dilute sodium bicarbonate solution, dried over magnesium sulfate, and evaporated to give 6.1 g (0.048 mol, 61%) of brown fluid, whose ir and nmr spectra were identical with those of 4-chlorotoluene.

Registry No.—**1**, 615-60-1; **2**, 2905-30-8; bis(3,4-dimethylphenyl) sulfone, 28361-43-5; 4-chlorotoluene, 106-43-4; *o*-xylene, 95-47-6; *p*-toluenesulfonyl chloride, 98-59-9.

The Cyclization of 2-Benzamido-1-phenyl-1-propanol to 1-Phenyl-3-methylisoquinoline

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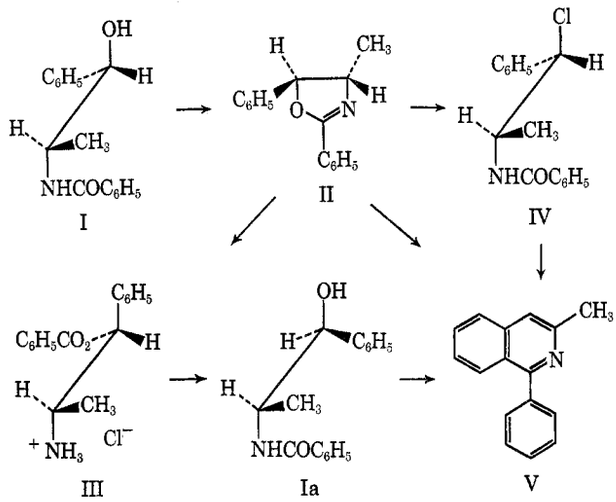
The cyclization of 3,4-diphenylbut-3-en-2-one oxime benzoate in nitrobenzene solution led unexpectedly to the formation of 1-phenyl-3-methylisoquinoline.[1] It was of great importance to us to confirm the identity of this cyclization product with a specimen obtained by a different route. The synthesis of 1-phenyl-3-methylisoquinoline by cyclization of 2-benzamido-1-phenyl-1-propanol given as a checked procedure,[2] based on the proposal earlier published,[3] furnished in our hands a product with mp 128–129°. On the other hand, our cyclization product obtained from 3,4-diphenylbut-3-en-2-one oxime benzoate had mp 89–90°, very close to that reported by Dobrovsky[4] and Gosh, *et al.*[5]

The uv, nmr, and mass spectra fully confirm the isoquinoline structure with the phenyl in the 1 and methyl in the 3 position. Our present task was to elucidate the structure of the compound obtained by Whaley and Hartung (mp 123–125°), quoted by Fitton and Smalley as having mp 126–127° and found by us to have mp 128–129°. In our opinion these were the same product, and the small differences in the melting points are caused by varying states of purity. The elemental analysis suggested the presence of oxygen and the data were in full agreement with those calculated for the starting material, 2-benzamido-1-phenyl-1-propanol. In addition the nmr spectrum was almost identical with that of starting amide and that of the product obtained after its treatment with P_2O_5 and $POCl_3$ in boiling xylene according to ref 2 and 3.

The only rational explanation is that the product claimed by Whaley and Hartung to be 1-phenyl-3-methylisoquinoline is in fact the threo isomer of the original erythro amide. The change of configuration in a series of analogous amides is well known.[6] The reaction pathways may be illustrated as follows.



The Whaley and Hartung product, in our opinion, is Ia, formed as a result of transformation I → II → III → Ia, and the reported derivatives were the hydrochloride and picrate of III. Our point of view has been confirmed by cyclization of both I and Ia in boiling decalin in the presence of phosphorus pentoxide. We have also synthesized 2,5-diphenyl-4-methyloxazoline (II) and 2-benzamido-1-chloro-1-phenylpropane (IV) and then we have refluxed them in decalin with P_2O_5. In all cases the only basic product was 1-phenyl-3-methylisoquinoline, mp 89–90°. The isolation of III after treatment of I with phosphorus oxychloride gives further support for our point of view. Our final conclusion, therefore, is that the cyclization of I does not take place under the conditions reported by Whaley and Hartung and quoted by Fitton and Smalley. The ring closure of 2-benzamido-1-phenyl-1-propanol takes place only when the amide is heated with phosphorus pentoxide at the much higher temperature of boiling decalin.

Experimental Section

Melting points were determined using a Thiele capillary melting point apparatus and are uncorrected. Uv spectra were determined with a C. Zeiss VSU-2P spectrophotometer, nmr spectra were recorded on a Tesla 80-MHz spectrometer, and ir spectra were recorded on a Unicam SP-200G spectrophotometer.

2-Benzamido-1-phenyl-1-propanol (I) was obtained from propiophenone by a three-stage synthesis according to ref 2: mp 143–144°; ir (Nujol) 3375, 3305 (NH, OH), 1640 (C=O), 1550 cm^{-1} (NH); nmr (DMSO-d_6) δ 1.05 (d, 3, CH_3), 4.13 (m, 1, C^2H), 4.69 (m, 1, C^1H), 5.39 (d, 1, OH), 7.08–7.88 (m, 10, aromatics), 8.12 (d, 1, NH).

2,5-Diphenyl-4-methyloxazoline (II) was obtained according

(1) S. Goszczyński and E. Salwińska, *Tetrahedron Lett.*, 3027 (1971).
(2) A. O. Fitton and R. K. Smalley, "Practical Heterocyclic Chemistry," Academic Press, New York, N. Y., 1968.
(3) W. M. Whaley and W. H. Hartung, *J. Org. Chem.*, **14**, 650 (1949).
(4) A. Dobrovsky, *Monatsh. Chem.*, **82**, 140 (1951).
(5) T. N. Gosh and B. Bhabatosh, *J. Indian Chem. Soc.*, **36**, 425 (1959).
(6) J. Farkas and J. Sicher, *Collect. Czech. Chem. Commun.*, **20**, 1391 (1955).