NMR δ 1.26, 1.31 (2d, 6 H, J = 6.0 and 5.5 Hz), 1.41–1.89 (m, 10 H), 2.35 (br t, 2 H), 3.54–4.16 (m, 3 H).

Isolation of the two diastereoisomers was achieved using a Varian Autoprep 705 gas chromatograph with a 9 mm × 2 m aluminum column of KOH-modified 20% polyethylene glycol 20M on Chromosorb W (60–80 mesh). The column temperature was held at 230 °C for 75 min and then was increased to 240 °C. A nitrogen flow rate of 150 mL/min was maintained throughout. The two samples obtained were chromatographed separately on alumina (grade III). Fractions eluted with 2:1 hexane–ether contained the pure products: NMR (diastereomer I) δ 1.28 (2d, 6 H, J = 5.5 Hz), 1.41–1.96 (m, 10 H), 2.33 (br t, 2 H), and 3.55–3.91 (m, 3 H); NMR (diastereomer II) δ 1.26 (d, 6 H, J = 6.0 Hz), 1.42–1.96 (m, 10 H), 2.32 (br t, 2 H), and 3.56–4.21 (m, 3 H).

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Registry No.—(±)-**1a**, 62989-38-2; (±)-**1b**, 62989-39-3; (±)-**1c**, 62948-63-4; (±)-**1d**, 21754-22-3; (±)-**1e**, 61949-75-5; (±)-**1f**, 62948-64-5; (±)-**2b**, 35221-77-3; (±)-**2g**, 35337-27-0; (±)-**2h**, 30665-84-6; (±)-**2i**, 28458-39-1; **3a** isomer 1, 62948-65-6; **3a** isomer 2, 62989-40-6; **3b** isomer 1, 62948-66-7; **3b** isomer 2, 62989-41-7; **3c** isomer 1, 62948-67-8; **3c** isomer 2, 62989-42-8; **3d** isomer 1, 62948-68-9; **3d** isomer 2, 62989-43-9; **3e** isomer 1, 62948-69-0; **3e** isomer 2, 62989-44-0; **3f** isomer 1, 62948-70-3; **3f** isomer 2, 62989-45-1; **4b** isomer 1, 62948-71-4; **4b** isomer 2, 62989-46-2; **4g** isomer 1, 62948-72-5; **4g** isomer 2, 63038-29-9; **4h** isomer 1, 62948-73-6; **4h** isomer 2, 62989-47-3; **4i** isomer 1, 62948-74-7; **4i** isomer 2, 62989-48-4; (−)-(2R,3R)-2,3-butanediol, 24347-58-8.

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(15) Attempts to extend the analysis to chiral γ-lactones using a variety of ortho ester synthetic methods[9–13] have not been successful.[16] Recently, an NMR method for determination of enantiomeric composition of γ-lactones was published: W. H. Pirkle, D. L. Sikkenga, and M. S. Pavlin, *J. Org. Chem.*, **42**, 384 (1977); W. H. Pirkle and D. L. Sikkenga, *ibid.*, **42**, 1370 (1977).
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The Pomeranz–Fritsch Reaction, Isoquinoline vs. Oxazoles

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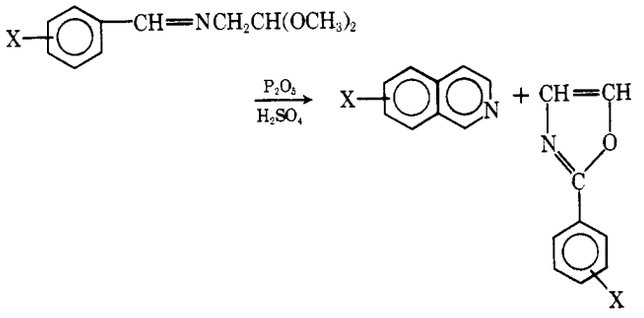
The Pomeranz–Fritsch reaction has been used for the preparation of a number of isoquinolines with varying yields.[1] As ordinarily carried out it involves the condensation of benzal aminoacetal to the isoquinoline. The yield varies from quite good with certain methoxy substituents to zero with nitro groups; in the latter case, the products are oxazoles.[2,3]



In this work we report the percent of oxazole formed with methyl, chloro, and nitro groups present in the original benzaldehyde. The Pomeranz–Fritsch reaction has been run with both o- and p-tolualdehyde. The yield of 8-methylisoquinoline in the first case is 18% and of 6-methylisoquinoline in the second case is 21%. We have also run the reaction with m-tolualdehyde and have obtained a yield of crude mixed 5- and 7-methylisoquinolines of 22%. A very careful search for 2-(tolyl)oxazole by chromatography and mass spectra analysis has shown yields of 3, 1, and 6%, in the cases of o-, m-, and p-tolaldehydes in the crude isolated products.

When acetals of the three chlorobenzaldehydes were subjected to conditions of the Pomeranz–Fritsch reaction, the oxazole production became appreciable. In the case of ortho it was 36% of the crude product isolated, in meta 23%, and in para 61%. The acetals of o-, m-, and p-nitrobenzaldehyde were cyclized and the yields were 54, 50, and 40%, respectively, of oxazole with no evidence for any isoquinoline. The three 2-nitrophenyloxazoles were then reduced and the amino compounds subjected to Sandmeyer[4] reactions to give the corresponding chloro compounds. These were then compared to the chlorophenyloxazoles formed by direct Pomeranz–Fritsch reaction (Table I).

Experimental Section

Separations were carried out on a Hewlett-Packard 5750 chromatograph with a 20 ft × ¼ in. column filled with Carbowax M on Anakrom 50/60 AB.

2-(x-Nitrophenyl)oxazoles. 2-(p-Nitrophenyl)oxazole (mp 163–164 °C) and 2-(o-nitrophenyl)oxazole (mp 43–46 °C) were prepared by the method of Cass and co-workers.[2,3] Heating 100 g (0.67 mol) of m-nitrobenzaldehyde and 70 g (0.67 mol) of dimethyl aminoacetal to 100 °C for 2 h and cooling gave a crude m-nitrobenzal aminoacetal. Twenty grams of this was dissolved in 100 mL of concentrated H_2SO_4, and poured into 40 g of P_2O_5 and 10 mL of H_2SO_4 at 180 °C and heated for 20 min. The solution was cooled and neutralized with NH_4OH to give 9 g (56%) of crude oxazole, mp 96–98 °C. Recrystallization from ethanol gave material with mp 97–98 °C, m/e (M^+) 190. Anal. Calcd for $C_9H_6N_2O_3$: C, 56.84; H, 3.15. Found: C, 56.88; H, 3.20.

2-(x-Aminophenyl)oxazoles. All three of the nitrophenyloxazoles above were hydrogenated in methanol with 10% Pd–C. 2-(o-Aminophenyl)oxazole[2] (mp 32–33 °C), 2-(p-aminophenyl)oxazole[3] (mp 121–123 °C), and the new 2-(m-aminophenyl)oxazole (mp 69–70 °C) were obtained.

Table I

Starting benzaldehyde	Registry no.	Isoquinoline	Registry no.	Pomeranz–Fritsch vs. oxazole: Total mixed, %	Pomeranz–Fritsch vs. oxazole: Oxazole/ isoquinoline	Registry no. of oxazole
o-Methyl	529-20-4	8-Methyl[5]	62882-00-2	18	3/97	62882-03-5
p-Methyl	104-87-0	6-Methyl[5]	42398-73-2	21	6/94	62882-04-6
m-Methyl	620-23-5	5- + 7-Methyl	62882-01-3 (5) 54004-38-5 (7)	22	6/94	62882-05-7
o-Chloro	89-98-5	8-Chloro[6]	34784-07-1	9	36/64	62881-98-5
p-Chloro	104-88-1	6-Chloro	62882-02-4	25–50	61/39	46047-24-9
m-Chloro	587-04-2	5- + 7-Chloro[7]	5430-45-5 (5) 34784-06-0 (7)	14	23/77	62882-06-8
o-Nitro	552-89-6			All oxazole[2]		62882-07-9
m-Nitro	99-61-6			All oxazole		35582-07-1
p-Nitro	555-16-8			All oxazole[6]		62882-08-0

Anal. Calcd for $C_9H_8N_2O$: C, 67.50; H, 5.00. Found: C, 67.49; H, 5.10.

2-(*x*-Chlorophenyl)oxazoles. The three aminophenyloxazoles (3-g samples) were subjected to Sandmeyer reactions.[4] 2-(*m*-Chlorophenyl)oxazole (mp 34–35 °C) was obtained after recrystallization from methylcyclohexane. The yield of crude compound before recrystallization was 3 g (90% of the theoretical).

Anal. Calcd for C_9H_6NOCl: C, 60.17; H, 3.34. Found: C, 60.05; H, 3.25.

2-(*p*-Chlorophenyl)oxazole, mp 80–81 °C after recrystallization. The crude product weighed 3.2 g (93% of the theoretical).

Anal. Calcd for C_9H_6NOCl: C, 60.17; H, 3.34. Found: C, 60.25; H, 3.30.

2-(*o*-Chlorophenyl)oxazole was a liquid, bp 130 °C (7.5 mm), picrate mp 114–115 °C. There was obtained 3 g (90% of the theoretical). The chlorophenyloxazoles were compared with those prepared by the Pomeranz–Fritsch reactions.

Anal. Calcd for C_9H_6NOCl: C, 60.17; H, 3.34. Found: C, 60.30; H, 3.10.

Pomeranz–Fritsch Reactions with Chloro Substituents. Pomeranz–Fritsch reactions were run on benzal aminoacetals from *o*-,[5,6] *p*-,[5] and *m*-chlorobenzaldehydes.[7]

The yields of chloroisoquinolines obtained were as indicated in the literature. However, the crude products in each case were separated on a Hewlett-Packard 5750 research chromatograph. The temperature was maintained at 240 °C with 30 psi He pressure. An 20-ft column containing 20% Carbowax 20M on Anakrom 50/60 AB was used and peaks were separated in collection tubes and submitted to mass spectrometry. Peaks for the respective aldehyde, its corresponding acid, the oxazole, and chloroisoquinoline were noted but only the oxazole and chloroisoquinoline were compared quantitatively. The yield of oxazole as compared to isoquinoline for *o*-chlorobenzal aminoacetal was 36% oxazole to 64% 8-chloroisoquinoline, for the meta 23% oxazole to 77% 5- and 7-chloroisoquinoline mixture, and for para 61% oxazole to 39% 6-chloroisoquinoline.

A crude dimethyl *p*-chlorobenzalaminoacetal (40 g, from equivalent weights of aldehyde and aminoacetal heated to 120 °C to remove water) was dissolved in 200 mL of concentrated H_2SO_4 at 5 °C, added to 80 g of P_2O_5 and 20 mL of H_2SO_4, and heated to 160 °C for an additional 20 min. The mixture was cooled, neutralized, and steam-distilled. An ether extract of the steam distillate was evaporated to dryness to give 10 g of crude material. This was first extracted with 13% aqueous HCl to remove 6-chloroisoquinoline, then with 38% HCl to remove the oxazole, leaving *p*-chlorobenzaldehyde.

2-(*p*-Chlorophenyl)oxazole. Analysis, see above; mixture melting point was correct.

6-Chloroisoquinoline. Anal. Calcd for C_9H_6NCl: C, 66.06; H, 3.67. Found: C, 66.10; H, 3.70.

Methylisoquinolines by the Pomeranz–Fritsch Reaction. *o*-Methylbenzalaminoacetal and *p*-methylbenzalaminoacetal have been cyclized by Pomeranz[5] to 8-methylisoquinoline and 6-methylisoquinoline, respectively. We have cyclized the *m*-methylbenzalaminoacetal to a mixture of 5- and 7-methylquinolines. *m*-Tolualdehyde and aminoacetaldehyde dimethyl acetal were heated in equivalent amounts to 120 °C until the water was removed. This crude product (50 g) was then dissolved in 250 mL of H_2SO_4 at 5 °C and this mixture added to a mixture of 75 g of P_2O_5 and heated at 160 °C for 25 min.

The reaction product was cooled, neutralized, and steam-distilled. The crude distillate was ether extracted and subjected to gas chromatography. The 5- and 7-methylisoquinoline mixture was extracted with dilute acid and recovered. It was possible to crystallize 6 g of 7-methylisoquinoline, melting at 66 °C from the 10 g of crude product. The yield of 2-(*m*-methylphenyl)oxazole was only 1% in this case.

Registry No.—Dimethyl aminoacetal, 22483-09-6; *m*-nitrobenzal aminoacetal, 62882-09-1; 2-(*o*-aminophenyl)oxazole, 62882-10-4; 2-(*p*-aminophenyl)oxazole, 62882-11-5; 2-(*m*-aminophenyl)oxazole, 35582-08-2; 2-(*o*-chlorophenyl)oxazole picrate, 62881-99-6; dimethyl *o*-chlorobenzalaminoacetal, 62882-12-6; dimethyl *m*-chlorobenzalaminoacetal, 62882-13-7; dimethyl *p*-chlorobenzalaminoacetal, 54879-73-1; dimethyl *o*-methylbenzalaminoacetal, 54879-71-9; dimethyl *p*-methylbenzalaminoacetal, 54879-70-8; dimethyl *m*-methylbenzalaminoacetal, 62882-14-8.

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Conjugate Addition of Grignard Reagents to Ethyl Acrylate

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The homologation of alkyl and aryl halides with a three-carbon chain terminating in a carboxyl or ester function is of some importance in synthesis,[1,2] and a variety of methods can be utilized to accomplish the transformation. Among these methods is the reaction of aryl and heterocyclic iodo compounds with the copper(I) salt of ethyl propiolate,[3] palladium-catalyzed vinylic hydrogen substitution reaction of methyl acrylate with aryl, benzyl, and styryl halides,[4] ethylenation of secondary and tertiary alkyllithiums, followed by carbonation,[5] alkylation of metalated α,β-ynamines with allyl and *n*-alkyl halides, followed by hydrolysis,[6] and conjugate addition of methyl propiolate with organocopper reagents[7] or mixed cuprate reagents.[8] These methods suffer, however, the following disadvantages. Firstly, although some of them give satisfactory yields, none of them has wide applicability, and furthermore, certain reagents, such as 1-propynyl-2,2,6,6-tetramethylpiperidine,[6] are not readily accessible. Secondly, when the product is an unsaturated ester, e.g., $CH_2{=}CHCH_2CH{=}CHCOOCH_3$,[7] subsequent hydrogenation