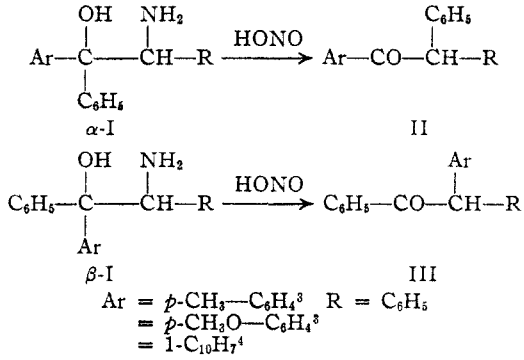
[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, COLUMBIA UNIVERSITY]

Stereospecificity in the Rearrangement of Aminoalcohols. II[1]

BY DAVID Y. CURTIN AND PETER I. POLLAK[2]

The two diastereoisomeric racemates of 1,2-diphenyl-1-*p*-chloro-2-aminoethanol and 1-phenyl-1-*p*-tolyl-2-aminopropanol have been prepared and rearranged by treatment with nitrous acid. In each case the α-racemate rearranges with almost exclusive migration of phenyl while the β-racemate rearranges with migration of the aryl group. The significance of these results is discussed and relative configurations are tentatively assigned to these molecules.

In a previous communication[3] it has been shown that the rearrangement of diastereoisomeric aminoalcohols (α-I and β-I, R = C_6H_5) with nitrous acid to ketones (II and III) was primarily determined by the configuration of the reacting molecule.



The present work has been carried out in order to gain further information about the extent of the observed stereospecificity as a function of the substituent of Ar and the steric size of R.

We have also synthesized the diastereoisomeric α- and β-racemates of 1-phenyl-1-*p*-tolyl-2-aminopropanol (α-I and β-I, Ar = *p*-CH_3-C_6H_4, R = CH_3) which had previously been prepared by Tiffeneau and his co-workers.[6] These authors state, "Ces deux diastéréoisomères ont été soumis à la déamination"[6] and report the formation of 4-methyl-α-phenylpropiophenone (II, Ar = *p*-CH_3-C_6H_4, R = CH_3). They did not isolate this compound, but claimed its identification by formation of a semicarbazone. It is thus implied, but not stated, that both diastereoisomers gave the same product.

We have observed that the rearrangement of these two diastereoisomers proceeds with stereospecificity in agreement with our previous results.[3] The racemic α-1-phenyl-1-*p*-tolyl-2-aminopropanol (α-I, Ar = *p*-CH_3-C_6H_4, R = CH_3) rearranged in agreement with Tiffeneau's report[6] with migration of the phenyl group to 4-methyl-α-phenylpropiophenone (II, Ar = *p*-CH_3-C_6H_4, R = CH_3). In the rearrangement of the racemic β-1-phenyl-1-*p*-tolyl-2-aminopropanol (β-I, Ar = *p*-CH_3-C_6H_4, R = CH_3) we could isolate only the isomeric α-*p*-tolylpropiophenone (III, Ar = *p*-CH_3-C_6H_4, R = CH_3) which was formed by migration of the *p*-tolyl group (Table I). These results differ from

TABLE I

REARRANGEMENT OF RACEMIC DIASTEREOISOMERIC AMINOALCOHOLS Ar—C(OH)(C6H5)—CH(NH2)—R

	Diastereoisomer	M. p., °C.	Rearrang. prod.	M. p., °C.	Yield of purified product, %
Ar = *p*-Cl-C_6H_4	α	158–159	*p*-Chlorophenyl benzhydryl ketone	108–109	60 (98)[a]
R = C_6H_5	β	155–156	α-*p*-Chlorophenyldesoxybenzoin	102–103	65 (89)
Ar = *p*-CH_3-C_6H_4	α	73–75[6]	4-Methyl-α-phenylpropiophenone	44–45[12]	42 (89)
R = CH_3	β	99–100[6]	α-*p*-Tolylpropiophenone	43–44	30 (75)

[a] The figure in parentheses indicates the yield based on unrecovered starting material.

We have prepared both diastereoisomeric α- and β-racemates of 1,2-diphenyl-1-*p*-chlorophenyl-2-aminoethanol (α-I and β-I, Ar = *p*-Cl-C_6H_4, R = C_6H_5) introducing a potential migrating phenyl group with an electron-withdrawing substituent in the para position.[5] These two compounds rearranged stereospecifically in agreement with our previously reported results.[3] The racemic α-diastereoisomer yielded *p*-chlorophenyl benzhydryl ketone (II, Ar = *p*-Cl-C_6H_4, R = C_6H_5) with migration of the phenyl group, while the racemic β-diastereoisomer afforded α-*p*-chlorophenyldesoxybenzoin (III, Ar = *p*-Cl-C_6H_4, R = C_6H_5) with migration of the aryl group (Table I).

TABLE II

OXIDATION OF RACEMIC DIASTEREOISOMERIC AMINOALCOHOLS Ar—C(OH)(C6H5)—CH(NH2)—R

	Diastereoisomer	Oxidn. prod.	M. p., °C.	Yield, %
Ar = *p*-Cl-C_6H_4	α	*p*-Chlorobenzophenone	77–78[a]	64
R = C_6H_5	α	Benzoic acid	119–121	48
	β	*p*-Chlorobenzophenone	77–78[a]	72
	β	Benzoic acid	119–120	44
Ar = *p*-CH_3-C_6H_4	α	*p*-Benzoylbenzoic acid	193–194[b]	72
R = CH_3	β	*p*-Benzoylbenzoic acid	194–195[b]	84

[a] Kollariz and Merz, *Ber.*, **6**, 547 (1873). [b] Meyer, *Monatsh.*, **28**, 1224 (1907).

(1) Abstracted from a thesis presented by Peter I. Pollak in partial fulfillment of the requirements for the Ph.D. degree at Columbia University.

(2) University Fellow, 1949–1950.

(3) Pollak and Curtin, THIS JOURNAL, **72**, 961 (1950).

(4) McKenzie and Wood, *Ber.*, **71**, 358 (1938).

(5) L. P. Hammett, "Physical Organic Chemistry," McGraw-Hill Book Co., Inc., New York, N. Y., 1940, p. 188.

(6) Tiffeneau, Lévy and Ditz, *Bull. soc. chim. France*, [5] **2**, 1871 (1935).

TABLE III

ALKALINE CLEAVAGE OF KETONES

Ketone	Acid	M. p., °C.	Yield, %	Hydrocarbon	Yield, %	Identified as
p-Chlorophenyl benzhydryl ketone	*p*-Chlorobenzoic	241–242	58	Diphenylmethane	85	2,2′,4,4′-Tetranitrodiphenylmethane[a]
α-*p*-Chlorophenyldesoxybenzoin	Benzoic	119–120	90	*p*-Chlorodiphenylmethane	97	*p*-Chlorobenzophenone[b]
4-Methyl-α-phenylpropiophenone	*p*-Toluic	180–181	42	Ethylbenzene	79	Benzoic acid
α-*p*-Tolylpropiophenone	Benzoic	120–121	89	*p*-Ethyltoluene	62	Terephthalic acid

[a] Schoepf, *Ber.*, **27**, 2318 (1894). [b] Ref. (*a*) in Table II.

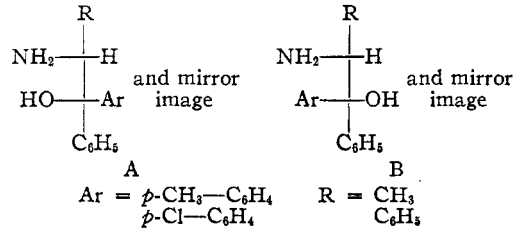
the indications of Tiffeneau,[6] but they are in agreement with the stereospecificity observed in the rearrangements of molecules of this type (α-I and β-I).

That the racemic pairs of aminoalcohols are stereoisomers rather than structural isomers was confirmed by oxidative degradation with alkaline permanganate. Both diastereoisomers of each aminoalcohol afforded identical oxidation products as shown in Table II.

The structures of the ketonic deamination products were supported by alkaline cleavage to acids and hydrocarbons as shown in Table III. The substituted isomeric propiophenones (II and III, Ar = *p*-CH_3-C_6H_4, R = CH_3) were not attacked by 25% methanolic potassium hydroxide, but adequate yields of the cleavage products could be obtained by treatment with 50% aqueous potassium hydroxide at 150–160°.

A possible explanation of this kind of stereospecificity has been discussed in the previous paper in this series.[3,7] The present work provides additional evidence that the electronic nature of the migrating group is of secondary importance since stereospecificity is observed with both electron-donating and electron-withdrawing substituents in the migrating groups. Our results show further that stereospecificity is retained even when one of the phenyls (R = C_6H_5) is replaced by the smaller methyl group (R = CH_3). In the case where R = C_6H_5, steric inhibition of resonance in the transition state may play a role,[3] but it seems as though this effect must be reduced in structures where R = CH_3 since there is only one non-migrating aryl in which resonance can be inhibited.

On the basis of this work it is possible to assign tentative configuration A to the α-racemates and configuration B to the β-racemates of the compounds below.



Experimental[8]

***dl*-α-1,2-Diphenyl-1-*p*-chlorophenyl-2-aminoethanol.**—To the ethereal solution of a Grignard reagent prepared from 14.2 g. (0.585 g. atom) of magnesium filings and 112 g. (0.585 mole) of *p*-chlorobromobenzene was added 18 g. (0.073 mole) of desylamine hydrochloride. The mixture was refluxed with agitation for 5 hours and decomposed with a mixture of ammonium chloride, concentrated ammonia and ice to yield 7.0 g. (30%) of *dl*-α-1,2-diphenyl-1-*p*-chlorophenyl-2-aminoethanol, m.p. (recrystallized from ethanol) 158–159°.

Anal. Calcd. for $C_{20}H_{18}ONCl$: C, 74.18; H, 5.60; N, 4.33; Cl, 10.95. Found: C, 74.40; H, 5.88; N, 4.30; Cl, 10.12.

An ethereal solution of the aminoalcohol was treated with gaseous hydrogen chloride to yield ***dl*-α-1,2-diphenyl-1-*p*-chlorophenyl-2-aminoethanol hydrochloride**, m.p. (recrystallized from ethanol) 223–224° with decomposition.

Anal. Calcd. for $C_{20}H_{19}ONCl_2$: C, 66.67; H, 5.32; N, 3.89; Cl, 19.62. Found: C, 66.47; H, 5.47; N, 3.60; Cl, 19.23.

α-Oximino-4-chlorodesoxybenzoin.—4-Chlorodesoxybenzoin, m.p. 106–107°[9] (recrystallized from ligroin), was obtained in 50% yield by a reaction of phenylacetyl chloride with chlorobenzene at 45° in presence of two equivalents of anhydrous aluminum chloride. An ethereal solution of 76 g. (0.33 mole) of crude 4-chlorodesoxybenzoin was treated with ethyl nitrite and gaseous hydrogen chloride,[10] and after extraction with 5% aqueous sodium hydroxide followed by acidification with ice-cold hydrochloric acid (1:1) there was obtained 61.0 g. (91%) of crude α-oximino-4-chlorodesoxybenzoin, m.p. 99–103°. A sample was recrystallized from carbon tetrachloride or ligroin to a constant melting point of 113–114°.

Anal. Calcd. for $C_{14}H_{10}O_2NCl$: C, 64.75; H, 3.88; N, 5.39; Cl, 13.65. Found: C, 64.84; H, 4.00; N, 4.97; Cl, 13.05.

4-Chlorodesylamine Hydrochloride.—A solution of 61 g. (0.24 mole) of crude α-oximino-4-chlorodesoxybenzoin in 520 ml. of 95% ethanol was poured into a solution of 305 g. of stannous chloride in 610 ml. of concentrated hydrochloric acid. After 48 hours the crystalline amine–tin complex was filtered and digested with 200 ml. of a saturated solution of sodium carbonate. The mixture was filtered and the residue extracted continuously with ether. The ether solution was dried with anhydrous sodium sulfate and treated with dry gaseous hydrogen chloride to yield 14.6 g. (22% of theory) of 4-chlorodesylamine hydrochloride, m.p. (recrystallized from ethanol) 251–252° with decomposition.

Anal. Calcd. for $C_{14}H_{13}ONCl_2$: C, 59.59; H, 4.64; N, 4.97; Cl, 25.13. Found: C, 59.29; H, 4.64; N, 4.72; Cl, 25.47.

***dl*-β-1,2-Diphenyl-1-*p*-chlorophenyl-2-aminoethanol.**—To an ethereal solution of a Grignard reagent prepared from 13.4 g. (0.55 g. atom) of magnesium and 78.5 g. (0.50 mole) of bromobenzene was added 14.0 g. (0.05 mole) of 4-chlorodesylamine hydrochloride in small portions. After 5 hours of refluxing the mixture was decomposed in the usual manner and the resulting solid recrystallized from ethanol to yield 5.80 g. (36%) of *dl*-β-1,2-diphenyl-1-*p*-chlorophenyl-2-aminoethanol, m.p. 155–156°, mixed m.p. with the α-racemate (m.p. 158–159°) 129–130°.

Anal. Calcd. for $C_{20}H_{18}ONCl$: C, 74.18; H, 5.60; N, 4.33; Cl, 10.95. Found: C, 74.46; H, 5.49; N, 4.19; Cl, 10.03.

***dl*-β-1,2-Diphenyl-1-*p*-chlorophenyl-2-aminoethanol hydrochloride** was prepared from the aminoalcohol by treat-

(7) The authors hope to present a more detailed discussion in a subsequent publication.

(8) All melting points are corrected. Elemental analyses were carried out by the Clark Microanalytical Laboratories, Urbana, Illinois.

(9) Jennings, THIS JOURNAL, **55**, 1618 (1933).

(10) "Organic Syntheses," Coll. Vol. II, John Wiley & Sons, Inc., New York, N. Y., p. 204.

ment with ethereal hydrogen chloride. The fine, white needles (recrystallized from ethanol) melted at 239–240° with decomposition.

Anal. Calcd. for $C_{20}H_{19}ONCl_2$: C, 66.67; H, 5.32; N, 3.89; Cl, 19.68. Found: C, 66.97; H, 5.55; N, 4.35; Cl, 18.95.

***dl*-α- and *dl*-β-1-phenyl-1-*p*-tolyl-2-aminopropanol.**—These compounds were prepared by the methods described by Tiffeneau, *et al.*,[6] and Behr.[11] The α-racemate melted after repeated recrystallization from ethanol at 76–77°, while Tiffeneau[6] reported a melting point of 65°. The compound gave the correct analysis for a hemihydrate.

Anal. Calcd. for $C_{16}H_{19}ON \cdot {}^1/_2H_2O$: C, 76.77; H, 8.05; N, 5.61. Found: C, 76.33; H, 7.87; N, 5.65.

The hemihydrate could be dehydrated by prolonged drying over phosphorus pentoxide at 56°. The resulting α-1-phenyl-1-*p*-tolyl-2-aminopropanol melted at 73–75° after repeated recrystallization from benzene or ligroin.

Anal. Calcd. for $C_{16}H_{19}ON$: C, 79.63; H, 7.94; N, 5.81. Found: C, 79.43; H, 7.95; N, 6.22.

Both the hemihydrate and the aminoalcohol yielded a hydrochloride, m.p. 252° with decomposition.[6]

Deamination of Diastereoisomeric Aminoalcohols (Table I).—The deamination of the racemic α- and β-1,2-diphenyl-1-*p*-chlorophenyl-2-aminoethanols and of the racemic α- and β-1-phenyl-1-*p*-tolyl-2-aminopropanols was carried out by a procedure described previously.[3] The deamination products obtained from the two diastereoisomeric aminopropanols were purified by chromatographic adsorption on activated alumina. The oils were dissolved in pentane and after deposition on the column eluted with redistilled benzene.

The *dl*-α-1,2-diphenyl-1-*p*-chlorophenyl-2-aminoethanol yielded 1.57 g. (60%) of *p*-chlorophenyl benzhydryl ketone, m.p. (recrystallized from ethanol) 108–109°.

Anal. Calcd. for $C_{20}H_{15}OCl$: C, 78.30; H, 4.93; Cl, 11.56. Found: C, 78.06; H, 4.73; Cl, 11.05.

(11) Behr, *Ber.*, **30**, 1521 (1897).

The β-racemate of this aminoalcohol yielded 1.43 g. (65%) of α-*p*-chlorophenyldesoxybenzoin, m.p. (recrystallized from ethanol) 102–103°. A mixed m.p. with *p*-chlorophenyl benzhydryl ketone (m.p. 108–109°) was 85–86°.

Anal. Calcd. for $C_{20}H_{15}OCl$: C, 78.30; H, 4.93; Cl, 11.56. Found: C, 78.29; H, 4.89; Cl, 11.77.

The deamination of the α-racemate of 1-phenyl-1-*p*-tolyl-2-aminopropanol afforded 1.139 g. (42%) of 4-methyl-α-phenylpropiophenone, m.p. (recrystallized from pentane) 44–45°.[6,12] A semicarbazone, m.p. 144–145°,[6,12] and an oxime, m.p. 123–124°,[12] were prepared from the ketone.

The *dl*-β-1-phenyl-1-*p*-tolyl-2-aminopropanol yielded upon deamination 0.820 g. (30%) of **α-*p*-tolylpropiophenone**, m.p. (recrystallized from pentane) 43–44°. A mixed melting point of this material with 4-methyl-α-phenylpropiophenone (m.p. 44–45°) was 2–5°.

Anal. Calcd. for $C_{16}H_{16}O$: C, 85.67; H, 7.19. Found: C, 85.75; H, 7.01.

An oxime of α-*p*-tolylpropiophenone, m.p. (recrystallized from ethanol) 153–155°, was prepared.

Anal. Calcd. for $C_{16}H_{17}ON$: C, 80.30; H, 7.16; N, 5.85. Found: C, 80.38; H, 7.14; N, 6.32.

A semicarbazone of this ketone could not be isolated.

Alkaline Cleavage of Deamination Products (Table III).—Cleavage of *p*-chlorophenyl benzhydryl ketone and the isomeric α-*p*-chlorophenyldesoxybenzoin was carried out by a procedure discussed elsewhere.[3] 4-Methyl-α-phenylpropiophenone and α-*p*-tolylpropiophenone were cleaved by heating with about fifty times the amount of 50% aqueous potassium hydroxide at 150–160° for a period of 45 hours in a copper test-tube. The hydrocarbon cleavage fragments were purified by deposition on activated alumina from a pentane solution and eluted with freshly distilled ligroin.

Structure of Diastereoisomeric Aminoalcohols (Table II).—The oxidative degradations were carried out by a procedure discussed previously.[3]

(12) Bruzeau, *Ann. chim.*, [11] **1**, 257 (1934).

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[CONTRIBUTION FROM THE DIVISION OF AGRICULTURAL BIOCHEMISTRY, UNIVERSITY OF MINNESOTA]

The Repeating Unit of Glycogen[1]

BY M. ABDEL-AKHER AND F. SMITH

Thirty-seven different samples of glycogen have been prepared. All were found to have a repeating unit containing approximately twelve anhydro-glucose residues. Glycogen with a repeating unit of 18 glucose residues was not encountered.

Investigations by several groups of workers into the methyl derivatives of specimens of glycogen obtained from a variety of sources have led to the conclusion that two types of glycogen occur in nature. The one most frequently obtained consists of repeating units containing about twelve glucose residues,[2a,2b,3,4] while the other, encountered much less frequently and apparently fortuitously, is said to contain approximately eighteen glucose residues in each repeating unit.[5–8]

Although it might not have been surprising to find that specimens of glycogen, obtained from the livers of animals fed a special carbohydrate diet such as D-galactose[7,8] would differ from the normal type, it seemed very curious, indeed, almost unbelievable, that this variation from the 12 to the 18 unit type should be encountered from time to time in commercial samples of liver glycogen prepared presumably from a number of normal rabbits.[5,8]

Since the evidence in favor of the 18 unit type of glycogen was derived from methylation studies which involved the isolation of the cleavage fragments of the methylated polysaccharide, it seemed conceivable that the high values were due to a loss of either the relatively volatile methyl-2,3,4,6-tetramethyl-D-glucoside or, less likely, to a loss of the corresponding tetramethyl sugar. This possibility, however, seemed to be ruled out by the fact that periodate oxidation also gave high values for the repeating unit when applied to the same samples of glycogen which had given a figure of 18 by the methylation technique.[8]

In a preliminary study of this apparent anomaly

(1) Presented in part before the Division of Sugar Chemistry and Technology at the Detroit Meeting of the American Chemical Society, April, 1950. Paper No. 2265, Scientific Journal Series, Minnesota Agricultural Experiment Station. This paper will form part of a thesis to be submitted by M. Abdel-Akher to the University of Minnesota in partial fulfillment for the degree of Ph.D.

(2) (a) Haworth and Percival, *J. Chem. Soc.*, 2277 (1932); (b) Bell, *Biochem. J.*, **29**, 2031 (1935); **31**, 1683 (1937).

(3) Haworth, Hirst and Smith, *J. Chem. Soc.*, 1914 (1939).

(4) Meyer and Fuld, *Helv. Chim. Acta*, **24**, 375 (1941).

(5) Haworth, Hirst and Isherwood, *J. Chem. Soc.*, 577 (1937).

(6) Bell, *Biochem. J.*, **30**, 1612, 2144 (1936).

(7) Bacon, Baldwin and Bell, *ibid.*, **38**, 198 (1944).

(8) Halsall, Hirst and Jones, *J. Chem. Soc.*, 1399 (1947).