Acetone Anil. Method A.[12]—Phenylammonium iodide (22.1 g.) and 47 g. of silver iodide were dissolved in 75 ml. of hot dimethylformamide, and 250 ml. of acetone was added. The solution was heated until the yellow color disappeared, then cooled to deposit white crystals which were collected and decomposed with a solution of 33 g. of potassium cyanide in 50 ml. of 20% potassium hydroxide. Extraction with ether gave 8.7 g. of crude acetone anil (65%).

(12) R. Kuhn and H. Schretzmann, *Angew. Chem.*, **67**, 785 (1955).

Method B.—The second method of preparation of acetone anil involved condensing aniline and acetone in the presence of a drying agent.[13] In the best run, 10 g. of aniline and 100 ml. of acetone were boiled in a Soxhlet extractor containing a thimble filled with potassium carbonate mixed with calcium sulfate to prevent lumping. After 23 hr., about two-thirds of the aniline had been converted to the anil according to g.l.c. analysis. The product could be isolated by careful fractional distillation.

(13) C. C. Tung, *Tetrahedron*, **19**, 1685 (1963).

The Configurational Relationships of the *cis*-β-Decalols and *cis*-β-Decalylamines[1]

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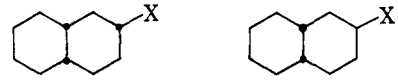
The question of the configurational relationships of the *cis*-β-decalols and *cis*-β-decalylamines has been unambiguously resolved by examining the products of ammonolysis of the tosylates of both alcohols. Cleanly inverted amines are obtained. The assignments of Dauben and Hoerger are shown to be correct. The suitability of the ammonolysis method for such configurational correlations is pointed out.

In recent years, there has been a great deal of interest shown in the stereochemistry of nitrous acid deaminations in cyclic systems.[2-8] In order to interpret the experimental data, it is usually necessary to know the configurational relationship between the epimeric pair of amines and the corresponding epimeric pair of alcohols. A classical method often used[9,10] to establish this relationship involves the expectation that the ratio of epimeric alcohols obtained by a given method of reduction of a cyclic ketone will be similar to the ratio of epimeric amines obtained upon similar reduction of the oxime of the ketone. It is then assumed that the predominant components of the two epimeric pairs are configurationally related.

Upon application of this method to the *cis*-β-decalols and *cis*-β-decalylamines, Hückel[9] found that hydrogenation of *cis*-β-decalone and its oxime, over a colloidal suspension of platinum in a solution of aqueous acetic acid containing hydrochloric acid, yielded rather homogeneous samples of an alcohol, m.p. 105°, and an amine (melting point of acetyl derivative 153°; melting point of benzoyl derivative 204°), respectively. The same two compounds predominated in the epimeric alcohol and amine mixtures when the ketone and oxime were reduced with sodium and alcohol. This alcohol and amine were thus assigned the same configuration, while the epimeric configuration was assigned to the minor components of the alkali reduction mixtures, an alcohol having a double melting point of 18 and 31° and an amine, the acetyl derivative of which melts at 88° and the benzoyl derivative at 128°.

Because these assignments did not lead to a consistent picture of the stereochemistry of the nitrous acid deamination of decalylamines, they were reinvestigated by Dauben and Hoerger.[11] These authors converted each of the *cis*-decalin-2-carboxylic acids to an alcohol by treatment with methyllithium followed by peracid oxidation and hydrolysis, and also to an amine by treatment of each acid with hydrazoic acid. These reactions are considered to be stereospecific, involving retention of configuration. As a result of this study, the original stereochemical assignments[9] were reversed. Dauben and Hoerger assigned the same configuration to the alcohol, m.p. 105° and acetamide, m.p. 88°.

Four years later, Hückel and Stelzer[10] reported a reinvestigation of this question. They repeated some of the earlier[9] reductions using improved analytical procedures and they carried out several reductions under new sets of conditions. In all cases the newer results supported the original assignments[9] and therefore appeared to contradict the assignments of Dauben and Hoerger.[11]



Dauben Assignment	
X = OH, m.p. 105°	X = OH, m.p. 18 and 31°
X = $NHCOCH_3$, m.p. 88°	X = $NHCOCH_3$, m.p. 153°
Hückel Assignment	
X = OH, m.p. 105°	X = OH, m.p. 18 and 31°
X = $NHCOCH_3$, m.p. 153°	X = $NHCOCH_3$, m.p. 88°

We now wish to report the results of experiments which establish the configurational relationships between the *cis*-β-decalols and the *cis*-β-decalylamines by a more direct means than the previous methods. The procedure is related in principle to those originally used[12] to establish stereochemical relationships in acyclic systems. It consists of converting each alcohol to its *p*-toluenesulfonate ester and converting the latter to

(1) This work was supported by Grant B-19 from the Health Research and Services Foundation, Pittsburgh, Pa.

(2) (a) A. K. Bose, *Experientia*, **9**, 256 (1953); (b) J. A. Mills, *J. Chem. Soc.*, 260 (1953).

(3) C. W. Shoppee, D. E. Evans, and G. H. R. Summers, *ibid.*, 97 (1957); C. W. Shoppee, R. J. W. Cremlyn, D. E. Evans, and G. H. R. Summers, *ibid.*, 4364 (1957).

(4) W. G. Dauben, R. C. Tweit, and C. Mannerskantz, *J. Am. Chem. Soc.*, **76**, 4420 (1954).

(5) A. Streitwieser, Jr., and C. E. Coverdale, *ibid.*, **81**, 4275 (1959).

(6) G. Drefahl and S. Huneck, *Ber.*, **93**, 1961, 1967 (1960).

(7) W. Hückel and K. Heyder, *ibid.*, **96**, 220 (1963).

(8) T. Cohen and E. Jankowski, Abstracts of Papers, 147th National Meeting of the American Chemical Society, Philadelphia, Pa., April, 1964, p. 47N.

(9) W. Hückel, *Ann.*, **533**, 1 (1938).

(10) W. Hückel and G. Stelzer, *Ber.*, **88**, 984 (1955).

(11) W. G. Dauben and E. Hoerger, *J. Am. Chem. Soc.*, **73**, 1504 (1951).

(12) A. J. H. Houssa, J. Kenyon, and H. Phillips, *J. Chem. Soc.*, 1700 (1929).

amine by subjecting it to ammonolysis at 100°. It has recently been shown[13] that ammonolysis of secondary *p*-toluenesulfonate esters in six-membered ring systems without participating neighboring groups results in elimination and substitution with clean inversion of configuration.[14]

The *cis-cis-* and *cis-trans* alcohols were obtained from a commercial mixture of the four β-decalols. Improved techniques for isolation of the latter compound in pure form from this mixture are described in the Experimental section. The purity of the *cis-cis*-2-decalol used was indicated by its melting point and that of the crude tosylate prepared from it. The purity of the *cis-trans*-2-decalol, which is a liquid at room temperature, was established by vapor phase chromatography.

Ammonolysis of each of the esters produced a different amine. That each amine was essentially homogeneous was shown by conversion to the acetyl derivative which was reasonably pure as obtained from the acetylation reaction mixture. The *p*-toluenesulfonate of the 105° alcohol, now thought to have the *cis-cis* configuration,[11] was converted to the acetamide, m.p. 153°, while that of the 18 and 31° alcohol was converted to the acetamide, m.p. 88°. Bearing in mind that these solvolyses occur with inversion of configuration, it is clear that the original[9,10] configurational assignments are incorrect and that the assignments of Dauben and Hoerger[11] are valid.

The method used here would appear to be the preferred one for the establishment of the configurational relationships of secondary alcohols and amines, at least in six-membered cyclic systems in which participating neighboring groups are not present.[15] The procedure is simple and exceedingly direct. It involves only two assumptions: that the formation of the ester from the alcohol proceeds with retention of configuration and that the ammonolysis proceeds with inversion of configuration. Neither of these can be seriously questioned in these systems. Furthermore, in the cases studied thus far[17] the amines obtained are homogeneous. This establishes a high degree of rigor in the method and avoids extensive purification procedures for the amides in which fractionation of epimers can occur.

Methods[3,9,10] involving the ratios of epimers obtained upon reduction of ketones and oximes are not only extremely tedious experimentally but, as demonstrated here, they are also of questionable validity and should probably be avoided until more understanding is achieved of the factors affecting the stereochemistry of such reductions.

Experimental[18]

cis-cis-**2-Decalol.**—A crude mixture (900 g.) of the four isomeric 2-decalols (L. Light and Co., Ltd., Colnbrook, Bucks, England) was dissolved in a minimum quantity of pentane at room temperature and cooled in a Dry Ice–acetone bath. The precipitated solid, m.p. 63–67°, which was very predominantly *trans-cis*-2-decalol, when recrystallized twice by dissolving in pentane at room temperature and cooling to the temperature of a salt–ice bath, afforded 272 g. of the *trans-cis* alcohol, m.p. 74–75° (lit.[19] m.p. 75°).

Upon evaporation under reduced pressure, the mother liquor yielded 560 g. (3.64 moles) of mixed decalols. The mixture was treated with 586 g. (3.95 moles) of phthalic anhydride and heated in an oil bath at 140–145° for 12 hr.[20] The molten mass was poured into 4 l. of boiling water and boiled with vigorous stirring for 1 hr. The mixture was filtered hot and the residue was submitted to an identical hot water extraction. The water-insoluble solid was repeatedly extracted with boiling petroleum ether (b.p. 90–100°) to leave an insoluble portion which was fractionally recrystallized from ethanol–ethyl acetate (90:10) to give 260 g. (0.86 mole) of *trans-cis*-2-decalyl phthalate, m.p. 184–186°. The mother liquor (A) was set aside for work-up of the *cis-trans*-2-decalol. Upon saponification of 175 g. of the solid phthalate with methanolic potassium hydroxide,[20] there was obtained 85.0 g. of *trans-cis*-2-decalol, m.p. 71–73°. The total yield of this alcohol, still not completely pure, was thus about 44%.

The portion (570 g., 1.89 moles) of the acid phthalate mixture which was soluble in petroleum ether (b.p. 90–100°) contained mainly the esters of *cis-cis*-2-decalol and *trans-trans*-2-decalol. Saponification, as above, produced 257 g. (1.67 moles) of oil, b.p. 141–143° at 31 mm., which partially solidified in a refrigerator. The solid, m.p. 99–103°, obtained upon filtration, was recrystallized once from petroleum ether (b.p. 90–100°) to give 15 g. of *cis-cis*-2-decalol, m.p. 105–106° (lit. m.p. 105°,[19] m.p. 104–105°[21]).

cis-trans-**2-Decalol.**—Since the tedious procedures of Hückel and co-workers for the isolation of pure *cis-trans*-2-decalol[20] and the preparation of pure *cis-trans*-2-decalyl *p*-toluenesulfonate[9,22] has on occasion even failed in their hands,[23b] two new approaches to the *cis-trans* isomer were developed. The melting points of the four isomeric 2-decalyl 3,5-dinitrobenzoates were reported recently.[23a] In this case only is the melting point of the ester of the *cis-trans*-decalol considerably higher than that of the difficultly separable *trans-cis*-decalol. This suggested that its ease of isolation and identification would be enhanced with this derivative.

The ethanol–ethyl acetate mother liquor (A) from the fractional recrystallization of the portion of acid phthalate which was insoluble in petroleum ether (b.p. 90–100°) was evaporated to dryness. The residue was extracted with 200 ml. of refluxing petroleum ether (b.p. 64–66°), triturated with several portions of this solvent at room temperature, and recrystallized from benzene. Saponification of this material, m.p. 135–142°, produced a mixture containing 66% *cis-trans*-2-decalol and 34% *trans-cis*-2-decalol.[24]

A. From the 3,5-Dinitrobenzoates.—To a solution of 8.0 g. (0.052 mole) of the two decalols in 40 ml. of dry benzene was added 18.0 g. (0.078 mole) of 3,5-dinitrobenzoyl chloride in one portion. The solution was heated at reflux for 5.5 hr. and then, after cooling to room temperature, magnetically stirred with 40 ml. of 5% sodium bicarbonate for 20 min. The organic layer was diluted with 30 ml. of benzene and 50 ml. of ethyl acetate, separated, and washed with 60 ml. of 5% sodium chloride–5% sodium bicarbonate solution. After removal by filtration of accumulated insoluble material, and washing twice with 30 ml. of 5% sodium bicarbonate, 30 ml. of 30% sodium chloride, and three times with 40 ml. of water, the organic layer was filtered

(13) J. L. Pinkus, G. Pinkus, and T. Cohen, *J. Org. Chem.*, **27**, 4356 (1962).

(14) Although the previous work[13] concentrated on ammonolysis of equatorial tosylates, one axial tosylate was also shown to give lower yields of cleanly inverted product; see ref. 13, footnote 31b. In the present case, both epimeric tosylates exist predominantly in the equatorial conformation.[2b]

(15) The results reported[16] for the ammonolysis of cholesteryl tosylate make it appear that homoallylic participation can lead to substitution with retention of configuration as well as to rearranged amine.

(16) P. L. Julian, A. Magnani, E. W. Meyer, and W. Cole, *J. Am. Chem. Soc.*, **70**, 1834 (1948); R. D. Haworth, J. McKenna, and R. G. Powell, *J. Chem. Soc.*, 1110 (1953); R. D. Haworth, L. H. C. Lunts, and J. McKenna, *ibid.*, 986 (1955).

(17) Those in the present paper and in ref. 13.

(18) Melting points were determined on a Kofler block utilizing polarized light and a stage-calibrated thermometer. The infrared spectra were taken on a Beckman IR-8 spectrophotometer with sodium chloride optics.

(19) W. Hückel and R. Mentzel, *Ann.*, **441**, 1 (1925); see also D. H. R. Barton, *Experientia*, **6**, 316 (1950).

(20) W. Hückel, R. Mentzel, E. Brinkmann, and E. Kamenz, *Ann.*, **451**, 109 (1927).

(21) I. Moritani, S. Nishida, and M. Murakami, *Bull. Chem. Soc. Japan*, **34**, 1334 (1961).

(22) W. Hückel and R. B. Rashingkar, *Ann.*, **637**, 20 (1960).

(23) (a) W. Hückel and D. Rücker, *ibid.*, **666**, 30 (1963); (b) see footnote 21, p. 37 of this ref.

(24) Analysis by vapor phase chromatography was carried out on an F and M Model 1609 gas chromatograph (flame ionization detector) using an 8 ft. × 0.25 in. stainless steel column packed with 22% Carbowax 20M on 60–80-mesh Neutraport S, employing a column temperature of 150°, and these gas flow rates—nitrogen, 32 ml./min.; hydrogen, 52 ml./min.; and air, 350 ml./min. Retention times for the *trans-cis-* and *cis-trans*-2-decalols were 34 and 44 min., respectively.

through Drierite, decolorized with activated carbon, filtered, and dried finally by distillation of a portion of the solvent. The solution was evaporated to dryness under reduced pressure to furnish 14.54 g. of white solid, softening at 108°, mainly melting at 114–116° with the remaining crystals gradually melting up to 137°. The crude product was mixed with 340 ml. of refluxing absolute alcohol and the hot mixture was filtered to afford 2.52 g. (crop 1) of broad needles, m.p. 141–145° with softening from 135°. The alcohol solution deposited at 20° additional solid (crop 2), 4.99 g., m.p. 130–140° with softening from 125°. Crop 1 was dissolved in 135 ml. of refluxing absolute alcohol and was allowed to crystallize at 20° to give colorless needles (85% recovery), m.p. 142–148° with softening from 138°. Two recrystallizations from 135 ml. and 90 ml. of absolute alcohol gave 1.86 g. of needles, m.p. 146–148° with softening from 145°. The product was dissolved in 200 ml. of refluxing petroleum ether (b.p. 64–66°) and the solution was concentrated to 90 ml. by distillation. Cooling to 20° afforded the *cis-trans*-2-decalyl 3,5-dinitrobenzoate as sturdy needles, 1.61 g., m.p. 148–149° with slight softening from 143°, (lit.[23a] m.p. 151–152°). A second recrystallization from petroleum ether afforded 1.53 g. of ester with unchanged melting point. Crop 2, after three recrystallizations from absolute alcohol and one recrystallization from petroleum ether (b.p. 64–66°) afforded 3.40 g. of ester, m.p. 147–149° with softening from 144°. The recrystallized ester crops were saponified without further purification.

To a warm solution of 36 g. of potassium hydroxide in 350 ml. of ethanol was added 3.40 g. (9.76 mmoles) of *cis-trans*-2-decalyl 3,5-dinitrobenzoate. An immediate brilliant crimson color appeared which after a few minutes turned to brown-maroon. Most of the added ester did not dissolve. The mixture was maintained at reflux for 9 hr. Water (70 ml.) was then added and refluxing was continued for 3 hr. After cooling, the reaction mixture was mixed with 1500 ml. of water and 450 ml. of ether. The yellow-red ether layer was separated and the red aqueous layer was extracted twice with 350 ml. of ether. The combined ether extracts were washed three times with 150 ml. of water. Treatment of the light yellow ether solution with activated carbon gave a colorless solution, which was dried over Drierite and evaporated under reduced pressure to afford 1.30 g. (86%) of 2-decalol; v.p.c. analysis showed *cis-trans*-2-decalol 97%, *trans-cis*-2-decalol 3%.

Final purification could be achieved by gas chromatography (described later) or, with rather low efficiency, by adsorption chromatography. Preliminary experiments with columns of Woelm alumina, activity grade III (Alupharm Chemicals, New Orleans, La.), Florisil (Floridin Co., Tallahassee, Fla.), and silica gel indicated that the former two adsorbents furnished initial eluates slightly enriched in the *cis-trans*-2-decalol. A preparative run was thus carried out employing a dry-packed column (2.5 × 64 cm.) containing 190 g. of Florisil (60–100 mesh) which had been prewashed with 300 ml. of 1:4 benzene–petroleum ether (b.p. 64–66°). A solution of 1.30 g. of the decalol in 4 ml. of this same solvent mixture was placed on the column. Elution with 300 ml. of this solvent, followed by 500 ml. of a 1:1 mixture of the same two components gave trace amounts of unidentified oil (fractions 1–5). Elution with 535 ml. of benzene–petroleum ether (3:1) and 500 ml. of benzene afforded no products (fractions 6–14). Further elution with ether–benzene (1:4) gave fractions 15–21 (100 ml. each). The pure *cis-trans*-2-decalol emerged from the column with the benzene holdup (fraction 15). Fractions 15 and 16 contained pure *cis-trans*-2-decalol, 53 and 131 mg., respectively.[24] Fraction 17 contained 614 mg. of this decalol containing 2% of the *trans-cis* isomer. Fractions 18 and 19 contained 237 and 21 mg. of decalol, respectively. The latter was shown to contain 21% of the *trans-cis* isomer.

B. From Preparative V.p.c.—The 66:34 mixture of *cis-trans*- and *trans-cis*-2-decalols was conveniently separated on a Model A-700 Autoprep chromatograph (Wilkens Instrument and Research, Inc.) utilizing an aluminum column (20 ft. × 3/8 in.) packed with 30% SE-30 silicone gum rubber on 45–60-mesh Chromosorb P employing a column temperature of 172° and a nitrogen flow rate of 200 ml./min. The decalol mixture was dissolved in 2–4 parts by volume of benzene and injected either automatically in 0.40-ml. portions or manually in 0.25-ml. portions. Retention times for the *trans-cis*- and *cis-trans* isomers were 21 and 26 min., respectively. By collecting most of the desired peak, *cis-trans*-2-decalol, having the same purity (97%) as that obtained by using the 3,5-dinitrobenzoate method, was readily available. Several repetitions of the procedure afforded pure *cis-trans*-2-decalol.[24a]

***cis-cis*-2-Decalyl *p*-Toluenesulfonate.**—To a cooled (−10°) solution of 6.03 g. (0.0391 mole) of *cis-cis*-2-decalol (m.p. 105–106°) in 45.0 ml. of dry pyridine was added, in one portion with stirring and cooling, 16.5 g. (0.087 mole) of *p*-toluenesulfonyl chloride. The mixture was then removed from the cold bath and allowed to remain at room temperature for 8 hr. The mixture, containing suspended solid, was cooled to −10° and 15 ml. of distilled water was added in 1-ml. portions during a 5-min. period. The temperature was not allowed to rise above −5°. The mixture was poured on to about 100 g. of ice and then mixed with 200 ml. of chloroform. The organic layer was separated and washed with eight 100-ml. portions of 1 *N* sulfuric acid, one portion of aqueous sodium bicarbonate, and finally with water. The dried (sodium sulfate) organic layer was evaporated at 30° under reduced pressure and the residual oil was adsorbed on a column (25 × 1 cm.) of activated charcoal and Celite (3:2). Elution with petroleum ether (b.p. 64–66°) gave a pale yellow oil which solidified in a refrigerator. The crude tosylate (m.p. 77–79°) weighed 10.65 g. (88.3%). Recrystallization from pentane–ether (80:20) gave 9.5 g., m.p. 78–79° (lit.[3] m.p. 77–78°), of the *cis-cis* ester.

***cis-trans*-2-Decalyl *p*-Toluenesulfonate.**—A similar procedure was employed to convert 1.13 g. (7.30 mmoles) of the pure *cis-trans*-2-decalol into 1.99 g. (88.3% crude yield) of the *cis-trans* ester, m.p. 61–62.5°. The crude product was dissolved in a warm mixture of petroleum ether (b.p. 40–43°) and ether (20:1) and thoroughly cooled in a refrigerator. Filtration afforded 1.70 g. (75.2%) of fine needles, m.p. 64.5–65.0° (lit.[9] m.p. 65°).

Ammonolysis of *cis-cis*-2-Decalyl *p*-Toluenesulfonate.—This reaction was performed according to the method previously described[13] with the exceptions that a glass tube liner was used to minimize corrosion of the metal and that the bomb was flushed with nitrogen before it was charged with ammonia. A mixture of 1.54 g. (5.0 mmoles) of the ester and 43 ml. of anhydrous ammonia was sealed in the steel bomb and maintained at 100° in an oil bath for 100 hr. The residual solid obtained upon evaporation of the ammonia was washed out of the glass tube with 15 ml. of 2 *N* sodium hydroxide. After the addition of 30 ml. of water, the mixture was extracted with five 15-ml. portions of ether. One-half of this ether solution was extracted repeatedly with 0.5 *N* hydrochloric acid. The aqueous phase was made basic and extracted with ether. To the dried (potassium hydroxide) extract was added 5.0 ml. of acetic anhydride. After the solution had remained overnight in a closed container, the ether was removed and an excess of methanol was added to the residue in order to destroy excess acetic anhydride. Evaporation under reduced pressure, followed by addition of more methanol, and another evaporation, furnished 0.18 g. (37%) of pale yellow N-acetyl-*cis-trans*-2-decalylamine, capillary m.p. 152–153° (lit. m.p. 153°,[9] m.p. 154°[4]). Recrystallization from petroleum ether–ethanol removed most of the color and left the melting point unchanged.

Ammonolysis of *cis-trans*-2-Decalyl *p*-Toluenesulfonate.—The ammonolysis and acetylation were performed in the same way as for the *cis-cis* isomer. In order to remove suspected traces of acetic acid from the crude, oily amide, the latter was dissolved in ether and the solution was extracted with three 6-ml. portions of saturated sodium bicarbonate, 5 ml. of water, 8 ml. of 0.5 *N* hydrochloric acid, and three 5-ml. portions of water. The colorless ether solution was dried (potassium carbonate) and evaporated under reduced pressure to an oily residue which was insoluble in petroleum ether (b.p. 64–66°) but readily soluble in ether. A solution of this oil in petroleum ether containing a few per cent of ether was concentrated slowly in a stream of dry nitrogen. The residual viscous oil crystallized over a 1-day period.[25] From 522 mg. (1.69 mmoles) of ester there was obtained 67 mg.

(24a) NOTE ADDED IN PROOF.—Further evidence that each amine is uncontaminated by its epimer has now been obtained by vapor phase chromatography using a 13 ft. × 0.25 in. stainless steel column packed with 20% Carbowax 20 M on alkaline-washed, HMDS-treated Chromosorb W (110–120 mesh), at a column temperture of 175° and a helium flow rate of 38.4 ml./min. Single peaks were obtained for both the *cis-trans*-amine (retention time was 63.6 min.) and the *cis-cis*-amine (retention time was 72.0 min.).

(25) Hückel[9] refers to this acetyl derivative as "schlecht krystallisierenden."

(20.2%) of the crude N-acetyl-*cis*-*cis*-2-decalylamine, m.p. 82.5–84.0°. Recrystallization from petroleum ether–ether was conveniently performed at 0° and was initiated by seeding and continual scratching of the glass container with a thin glass rod. The acetamide was obtained as small, flat needles, m.p. 86–87° (lit.[9] m.p. 88°).

Notes

Deiodination of Iodophenyl Phenyl Ethers with Hydriodic Acid[1,2]

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Treatment of I with hydriodic acid to give the amino acid IIa is one of the well-established steps in the synthesis of thyroxine (IIb).[3] It has been found that the same conditions converted III to IV, but V gave VIa and not the expected VIb.[4] Meltzer, *et al.*,[5] have reported a similar type of reaction on treatment of β-[3-iodo-4-(4-methoxyphenoxy)phenyl]propionic acid with hydriodic acid; the deiodinated β-[4-(4-hydroxyphenoxy)phenyl]propionic acid was the only product isolated.

From these results, it appeared as if loss of iodine occurred most readily when one of the positions *ortho* to the ether oxygen was vacant. Therefore, a study was undertaken with some less-complex iodophenyl phenyl ethers to establish the relative ease of deiodination for various positions of iodine substitution. Treatment of 4-methoxyphenyl 2′-iodophenyl ether with hydriodic acid led to the deiodinated product, 4-hydroxyphenyl phenyl ether, in 89% yield. In order to separate involvement of the ether cleavage reaction from that of deiodination, the reaction of hydriodic acid with a series of iodophenyl phenyl ethers free of other substituents (Table I) was studied in greater detail by use of gas–liquid chromatography (g.l.c.). The ethers were heated under reflux (*ca.* 120°) for 5 hr. under different sets of conditions: (1) in an equivolume mixture of glacial acetic acid and 47% aqueous hydriodic acid, and (2) in the same system containing an excess of acetic acid. The conditions in 1 were those used in the thyroxine synthesis but gave a heterogeneous reaction mixture with the iodo ethers. The addition of an excess of acetic acid (method 2) gave a homogeneous reaction mixture. Following preliminary purification of the reaction mixture, the amounts of iodophenyl phenyl ether and the deiodinated products were estimated by g.l.c. The discussion that follows applies to both heterogeneous and homogeneous reaction conditions which gave similar results.

TABLE I

	$C_6H_5OC_6H_3XY$		Yield of diphenyl ether, %	
Compd.	X	Y	1[a]	2[a]
VII[b]	2-Iodo	H	60	69
VIII	3-Iodo	H	Trace	Trace
IX[b]	4-Iodo	H	100	100
X	2-Iodo	6-Iodo	0	2
XI[b]	2-Iodo	4-Iodo	7[c]	16[c]

[a] Refers to method 1 or method 2 (see Experimental). [b] Heated under reflux for 5 hr. in acetic acid alone, but no diphenyl ether could be detected by g.l.c. [c] 2-Iodophenyl and 4-iodophenyl phenyl ethers could be detected in the reaction mixture; their total per cent under method 1 was 14%. The individual isomers appeared to be in the ratio 1:1.

The reduction of aromatic iodo compounds by hydriodic acid in solution was first investigated in some detail by Shoesmith, *et al.*,[6] who showed that the ease of reduction of the isomeric iodophenols followed the sequence 4 > 2 ≫ 3; the series 2-, 4-, and 3-iodotoluenes was reduced with increasing difficulty in that order. We have found that the ease of reduction of the isomeric *monoiodophenyl* phenyl ethers (Table I, VII–IX) follows the same order as the isomeric phenols, 4 > 2 ≫ 3. As might be expected from a comparison of the steps I → IIa and V → VIa, the 2,6-diiodo compound X was recovered mainly unchanged, whereas the 2,4-diiodo derivative XI was partially reduced to a mixture of the monoiodo isomers and diphenyl ether.

The differences in the ease of reduction of these iodo compounds by hydriodic acid are best explained within the context of a reasonable reaction mechanism. Although the use of hydriodic acid to replace iodine with hydrogen in organic compounds has been known for some time, very little evidence has been accumulated for the mechanism and identity of the attacking species. A kinetic study on the action of hydriodic acid on some substituted *p*-iodophenols has been carried out by Gold and Whittaker[7] who concluded that the reduction is an electrophilic displacement of iodine, but they did not identify the attacking species. Recently it has been postulated that the acid-catalyzed deiodination of iodo aromatic compounds proceeds *via* the formation of

(1) Presented in part at the 148th National Meeting of the American Chemical Society, Chicago, Ill., Sept., 1964.

(2) Part XII of a series "Thyroxine Analogs." For part XI of this series, see ref. 4.

(3) J. R. Chalmers, G. T. Dickson, J. Elks, and B. A. Hems, *J. Chem. Soc.*, 3424 (1949).

(4) E. C. Jorgensen and J. A. W. Reid, *J. Med. Chem.*, **7**, 701 (1964).

(5) R. I. Meltzer, S. Farber, E. Merrill, and A. Caro, *J. Org. Chem.*, **26**, 1413 (1961).

(6) (a) J. B. Shoesmith, A. C. Hetherington, and R. H. Slater, *J. Chem. Soc.*, 1312 (1924); (b) J. B. Shoesmith and R. H. Slater, *ibid.*, 2278 (1924).

(7) V. Gold and M. Whittaker, *ibid.*, 1184 (1951).