tetrachloride solution of bromine slowly, and reduced alcoholic silver nitrate rapidly as evidenced by the formation of a silver mirror.

CONTRIBUTION NO. 467 FROM THE CENTRAL RESEARCH DEPARTMENT
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1,5-Anhydro-β-D-ribofuranose from Phenyl β-D-Ribofuranoside

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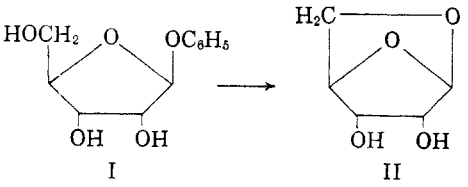
While the action of strong alkali on aryl glycopyranosides represents a familiar procedure for the synthesis of 1,5-anhydroglycopyranoses[2] and other analogous substances containing this ring system, similar treatment of aryl glycofuranosides has not, to our knowledge, been reported to yield 1,5-anhydroglycofuranoses. In a recent paper,[3] indeed, we stated that an attempt to synthesize 1,5-anhydro-β-D-ribofuranose (II, 1,4-anhydro-α-D-ribopyranose) from phenyl β-D-ribofuranoside (I) had



I II

failed to yield a crystalline product. Subsequent work has now shown, however, that I is converted to II (albeit in low yield) through the action of sodium isopropoxide in 2-propanol.

EXPERIMENTAL[4]

Phenyl β-D-ribofuranoside (158 mg.), prepared as described earlier,[3] was dissolved in 10 ml. of 2-propanol and the solution treated with 6 ml. of 2-propanol in which 32.5 mg. of sodium had been dissolved. The reaction mixture was boiled under reflux for 90 hr., cooled, diluted with a few drops of water and neutralized with carbon dioxide. Solvent was removed *in vacuo* and the residue extracted with acetone. Toluene was added to the extract and the solution concentrated *in vacuo* to a sirup which was freed of the remaining phenol by repeated extraction with benzene. Attempts to crystallize the residue failed and it was therefore benzoylated in the usual fashion to yield a sirup which was partially purified by precipitation from benzene with pentane and then from ethanol with water. On standing for several months at −8° in aqueous ethanol a small deposit of crystalline material was obtained. Recrystallized from methanol this product (*ca.* 15 mg., 6%) showed a double melting point: 132–133° and 146–147°. We reported earlier[3] that 1,5-anhydro-2,3-di-*O*-benzoyl-β-D-ribofuranose melts at 132–133°. Reexamination of the authentic material now reveals that it too shows the double melting point just quoted; a mixture of samples of the compound from the two sources shows the same two melting points. Upon appropriate seeding, either the form with the double melting point or one with the higher melting point only could be obtained from solution.

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(2) *Cf.* L. C. Stewart, E. Zissis, and N. K. Richtmyer, *Chem. Ber.*, **89**, 535 (1956).

(3) E. Vis and H. G. Fletcher, Jr., *J. Am. Chem. Soc.*, **79**, **1182** (1957).

(4) Melting points are corrected.

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Reciprocal Resolution of DL-Tryptophan and DL-α-Phenylethylamine

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Our interests in producing large quantities of L-tryptophan from the DL-form by economically feasible methods prompted a study of known methods and a search for new methods of resolution. The availability of *N*-acetyl-DL-tryptophan as an intermediate in commercial synthesis and the ease of racemization of the undesired D-form[1] indicated that this would be the desirable starting compound. Published methods[1–6] for resolving *N*-acetyl-DL-tryptophan suffer from one or more of the usual disadvantages of resolutions; such as, low yields, time consuming and tedious crystallizations, expensive resolving agents, or handling of large volumes. The method of du Vigneaud and Sealock[1] appeared to offer possibilities for attainment of maximum antipodal purity and for large scale use. The main disadvantage was the scarcity of the desired active form of α-phenylethylamine. DL-α-Phenylethylamine is readily available. If one were able to resolve this with the active forms of acetyltryptophan it would be possible to build up large supplies of optically active acid and base by repetition of the reciprocal resolution.

When one mole of *N*-acetyl-DL-tryptophan was combined with 0.5 mole of (−)- α-phenylethylamine and 0.5 mole of potassium hydroxide in ethanol the sparingly soluble diastereoisomeric salt [LA(−)B]

(1) V. du Vigneaud and R. R. Sealock, *J. Biol. Chem.*, **96**, 511 (1932).

(2) C. P. Berg, *J. Biol. Chem.*, **100**, 79 (1933).

(3) A. C. Shabica, *J. Am. Chem. Soc.*, **71**, 3251 (1949).

(4) Usines Chemiques des Laboratoires Francais, Brit. Patent **745,097**, Feb. 22, 1956; U. S. Patent **2,797,226**, June 25, 1957.

(5) C. Neuberg and I. Mandl, U.S. Patent **2,511,867** (Interchemical Corp.) June 20, 1950.

(6) D. G. Doherty and E. A. Popenoe, Jr., *J. Biol. Chem.*, **189**, 447 (1951).

crystallized in 73% yield and of purity greater than 99% without further recrystallization. The soluble *N*-acetyl-D-tryptophan was racemized with acetic anhydride and again resolved. The acetyl derivative was hydrolyzed to L-tryptophan or reserved for resolution of α-phenylethylamine as needed. The diastereoisomeric (−)-amine salt crystallized from ethanol in 99% purity and 83% yield when the DL-form was mixed with 0.5 equivalent of *N*-acetyl-L-tryptophan and 0.5 equivalent of hydrochloric acid.

Our starting materials were 60.5 g. of (−)-α-phenylethylamine[7] and a plentiful supply of *N*-acetyl-DL-tryptophan and DL-α-phenylethylamine. By alternately resolving acid and base with the available quantities of each several times it was easily shown that 12.5 kg. of acetyl-L-tryptophan and 8.6 kg. of (−)-α-phenylethylamine could be realized after 17 reciprocal resolutions. Thus it is rather easy to work up to quite large scale resolutions with no initial large supply of resolving agent.[8]

These particular experiments were directed toward production of L-tryptophan. Through suitable modifications D-tryptophan and derivatives could be made equally readily, if desired.

EXPERIMENTAL

I. Resolution of acetyl-DL-tryptophan. A. Formation and separation of the diastereoisomers. Acetyl-DL-tryptophan[9] (246 g., 1.0 mole) was dissolved in 500 cc. of hot *N* KOH in 95% 3A ethanol. To the warm solution there was added 60.5 g. (0.5 mole) of (−)-alpha-phenylethylamine.[7] The solution was allowed to cool overnight at room temperature. The yield of crystalline salt [LA(−)B] was 134 g. (73%), $[\alpha]_D^{25}$ + 17.8° (C, 2 in water).[10]

B. Decomposition of the less soluble salt [LA(−)B]. The salt (134 g.) was suspended in about 250 cc. of water and about 50 cc. of benzene. The mixture was made alkaline to phenolphthalein with sodium hydroxide. The aqueous phase was separated and washed three times with 50-cc. portions of benzene. The combined benzene extracts were washed once with water which was combined with the aqueous phase.

C. Preparation of L-tryptophan. The aqueous solution of the sodium salt obtained as in Ib was adjusted with water and 3 equivalents of hydrochloric acid to be 2*N* with respect to acidity. After heating under reflux for 4 hr. the solution was decolorized with carbon and evaporated to dryness under reduced pressure. The residue was extracted with 95% 3A ethanol to separate the tryptophan hydrochloride from the sodium chloride. The alcoholic solution was neutralized with ammonium hydroxide to precipitate the L-tryptophan. This was removed by filtration, washed on the funnel with water followed by alcohol, and dried. The yield was 95%; $[\alpha]_D^{25}$ −31.2° (C, 1 in water).

D. Recovery of acetyl-L-tryptophan. The aqueous solution from Ib was decolorized with activated carbon as necessary and acidified to *p*H 3 with hydrochloric acid. About 96% of the acetyl-L-tryptophan precipitated. This was removed by filtration, washed with water and dried. $[\alpha]_D^{25}$ + 29.1° (C, 1 in H_2O + 1 equivalent NaOH).

E. Decomposition of the more soluble salt and racemization of acetyl-D-tryptophan. The alcoholic solution from Ia was evaporated to dryness and the residue dissolved in about 250 cc. of water and the salt decomposed with NaOH as in Ib. The aqueous solution was decolorized with activated carbon as necessary and 150 cc. of acetic anhydride added. The solution was seeded with *N*-aectyl-DL-tryptophan and kept at 40° overnight, whereupon acetyl-DL-tryptophan crystallized in about 92% yield. After chilling the mixture, the crystalline product was removed by filtration, washed with water, and dried. Specific rotation was zero, m.p. 205–206° (uncorr.). The yield of product was increased to 97% by combining similar filtrates and obtaining additional crops after evaporation of solvent.

II. Resolution of DL-α-phenylethylamine. *N*-Acetyl-L-tryptophan (123 g., 0.5 mole) was dissolved in 250 cc. of warm 95% 3A ethanol. To this solution there was added 0.5 mole of concentrated hydrochloric acid followed by 121 g. (1.0 mole) of DL-α-phenylethylamine (prepared from acetophenone using formamide and formic acid as described by Moore[11]). The solution was seeded and allowed to crystallize at room temperature overnight. The yield of LA(−)B salt was 151 g. (83%), $[\alpha]_D^{25}$ +17.7° (C, 2 in water).[7] The salt was decomposed as in Ia. The (−)-amine was recovered by drying the benzene extracts over sodium hydroxide pellets and distilling the benzene and amine through a short column; b.p. 185–187°, $[\alpha]_D^{25}$ −38.8° to −39.3° (without solvent) depending upon whether the salt was recrystallized before decomposition.

The more soluble material from the original alcohol filtrate was decomposed as in Ie to recover *N*-acetyl-L-tryptophan and the amine rich in the dextro-rotatory form.

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(7) We are indebted to Professor A. W. Ingersoll of Vanderbilt University for this initial supply of active amine.

(8) Although it was not investigated in this study it is also possible to obtain an initial large supply of (−)-α-phenylethylamine through the method of DeWitt and Ingersoll using easily available *N*-acetyldibromo-L-tyrosine, *J. Am. Chem. Soc.*, **73**, 5782 (1951).

(9) Purchased from the Winthrop Chemical Co.

(10) Recrystallization from water increased the specific rotation of the salt to +18.8°, which was unchanged by further crystallization. The over-all yield of salt was reduced to 64%. Unless a product of exceptional antipodal purity was desired recrystallization was normally omitted.

(11) M. L. Moore, *Org. Reactions*, **5**, 321 (1949).

Preparation of 3-(1,1,2-Trifluoro-2-chloroethoxy)propanol and Some of Its Derivatives

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The preparation of ethers of the general formula RO—CF_2—CX_2H where R is an alkyl radical and X is halogen or hydrogen has received a good deal of attention in recent years.[2–4] However, very little has been done in the preparation of ethers of the type, $OH(CH_2)_n$-O-CF_2CX_2H. Coffman *et al.*[5]

(1) Abstracted from a thesis submitted by J. G. Abramo in partial fulfillment of the requirements for the Ph.D. degree, University of Colorado, June 1956.

(2) J. D. Park, D. K. Vail, and J. R. Lacher, *J. Am. Chem. Soc.*, **70**, 1550 (1948).

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