two molar equivalents of hydrogen was absorbed in twenty minutes, after which no more was absorbed. The reaction mixture was taken up in acetone, filtered and distilled. Redistillation of the fore-run gave 3.4 g. of *n*-butanol (27% yield), identified by odor, boiling point (116.5–117.5°) and refractive index ($n^{25}D$ 1.3970). The amount obtained was less than the actual yield due to accidental loss of part of the fore-run. The main distillate, a solid weighing 24 g., was collected at 117–146° (1.0 mm.). It proved to be a mixture of 2-naphthol and 1-*n*-butyl-2-naphthol, with over half of it by weight the former. Fairly pure samples of each, melting at 120–121° and 77–80°, respectively, were isolated by fractional crystallization from hexane, but complete separation by this means was not practical.


## Summary

Four 1-alkyl-1,2,3,4-tetrahydro-2-naphthols have been prepared by hydrogenation of the corresponding 1-alkyl-2-naphthols over copper chromite.

Instead of undergoing the Claisen rearrangement, β-methylallyl 2-naphthyl ether rearranges to what is believed to be a dihydronaphthofuran. Hydrogenation of 1-*n*-butyro-2-naphthol gives *n*-butanol and 2-naphthol besides the expected 1-*n*-butyl-2-naphthol.


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[CONTRIBUTION FROM THE COBB CHEMICAL LABORATORY, UNIVERSITY OF VIRGINIA]

# Arylcycloalkylamines. I. 2-Phenylcyclopropylamine

BY ALFRED BURGER AND WILLIAM L. YOST[1]

Both 1-phenyl-2-aminopropane and 1-amino-2-phenylpropane exhibit such striking effects on the central nervous system that structural variations of these drugs have received wide attention. It appeared of interest to investigate what changes in the pharmacological action of these drugs would result from the incorporation in a ring of the two-carbon chain separating the aryl from the amino group. The cyclopropyl ring was chosen as the first example because of the known analgesic and anesthetic properties of cyclopropane, cyclopropyl methyl ether (Cyprome), cyclopropyl ethyl ether (Cypreth), cyclopropylcarbinol, and related compounds.[2] It has been suggested[3] that "alicyclic residues might confer desirable pharmacological properties if introduced into compounds containing auxapharm groups. . . ." The auxapharm group in the compounds under consideration in this article is the phenethyl group.

The synthesis of the geometrically isomeric 2-phenylcyclopropylamines is reported here. The starting material was ethyl 2-phenylcyclopropanecarboxylate which had first been obtained by Buchner and Geronimus[4] from the condensation of styrene with ethyl diazoacetate. These authors heated the reagents in a sealed tube and had to cope with the high pressures of nitrogen from the reaction. These conditions were improved in the present work by slowly dropping a stoichiometric mixture of the diazo ester and styrene into an excess of styrene at 125°. Fractionation of the reaction mixture yielded from 75 to 85% of ethyl 2-phenylcyclopropanecarboxylate as a colorless oil of b. p. 103–105° (0.5–0.7 mm.).

Buchner and Geronimus hydrolyzed their ester to an acid of m. p. 105° to which they assigned the structure of *trans*-2-phenylcyclopropanecarboxylic acid. They arrived at this conclusion by nitrating their acid, reducing the nuclear nitro group, and oxidizing the resulting aminophenylcyclopropanecarboxylic acid with permanganate to *trans*-cyclopropanedicarboxylic acid. When we saponified our ester, a mixture of two isomeric carboxylic acids was always obtained which could be separated by fractional crystallization from water. The less soluble material, which we designate as 2-phenylcyclopropanecarboxylic acid A, crystallized as slender needles, m. p. 93°, and represented 74% of the total mixture.

Benzene extraction of the mother liquors of this acid yielded about 13% of a material melting at 106–107° for which we propose the name of 2-phenylcyclopropanecarboxylic acid B. Its identity with that described by the earlier investigators was corroborated by conversion of its chloride to the amide of m. p. 187–188° [190–191°(cor.)]. The amide reported in the literature[4] melts at 187–188°.

The relation of the two acids was established when it was found that the acid chloride of either product may be hydrolyzed to the A-acid, or ammonolyzed to the same amide of m. p. 190–191°. This indicates that the B-acid is probably inverted by thionyl chloride to the same acid chloride as that obtained from the A-acid, but the less likely possibility must be considered that a B-acid chloride first formed is inverted to derivatives of the A-series by hydrolysis or ammonolysis. These observations coupled with the predominant formation of the A-acid in their preparation from styrene, permit the conclusion that the acid of m. p. 93° is the more stable of a pair of geometrical isomers. It should be noted that the amide described by Buchner and Geronimus is a derivative of the lower-melting isomer they never isolated.

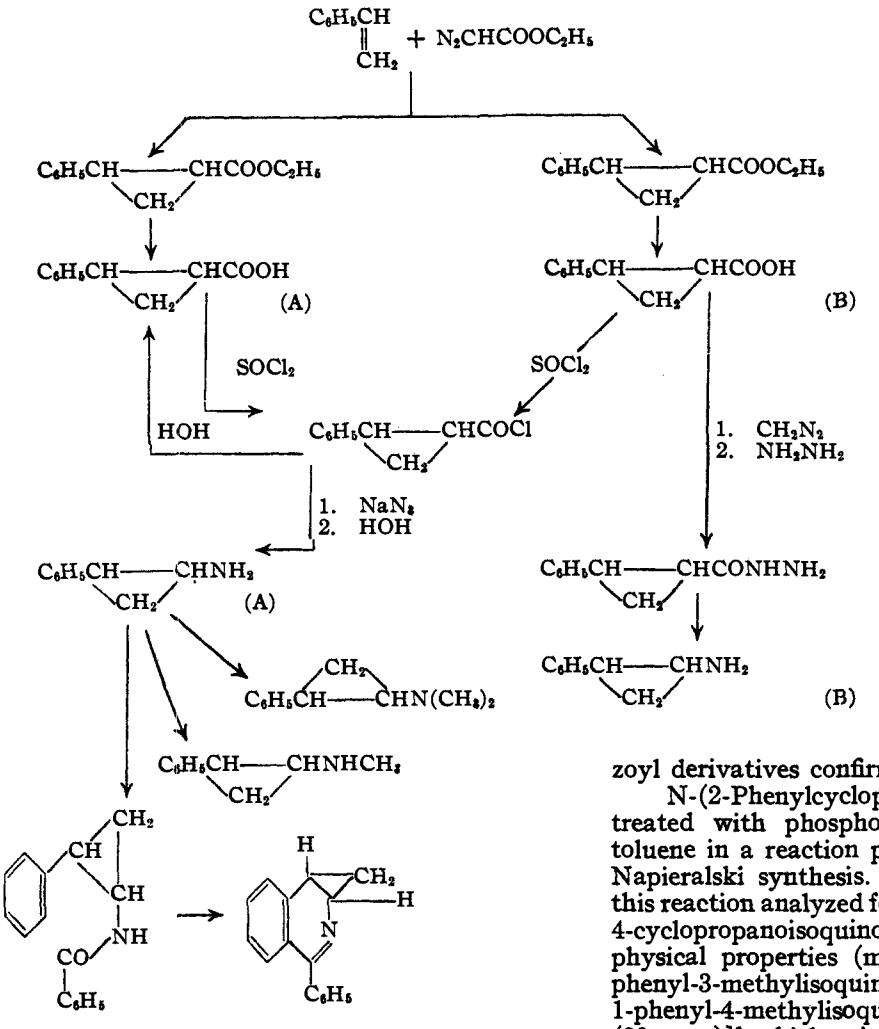
We considered the possibility that the addition of ethyl diazoacetate to styrene might have led to esters containing the ethylenic bond. This is, however, unlikely because the presence of the cy-

(1) Smith, Kline and French Laboratories Fellow.

(2) Adriani, "The Chemistry of Anesthesia," Charles C. Thomas, Publisher, Springfield, Ill., 1946, pp. 130, 174.

(3) Braker, Pribyl and Lott, THIS JOURNAL, 69, 866 (1947).

(4) Buchner and Geronimus, *Ber.*, 36, 3782 (1903).



clopropane ring system had already been established[4] for the acid melting at 106–107°, and the acid A can be obtained from it by means of reagents which are known not to open the cyclopropane ring.

The absolute configuration of the isomeric 2-phenylcyclopropanecarboxylic acids has not been established with certainty. The greater stability of the A-isomer casts some doubt on the previous assignment of the *trans* configuration to the B-isomer. The isomerization of the higher- to the lower-melting isomer by thionyl chloride is in accord with the general ease of conversion of *cis* to *trans* isomers by acids, acid halides, etc.

2-Phenylcyclopropane carboxamide A withstood Hofmann degradation under a number of experimental variations, and no amine could be obtained in this manner. Likewise, the A-acid (m. p. 93°) did not respond to the Schmidt reaction. However, it was found possible to subject its chloride to the Curtius degradation with sodium azide in boiling toluene; the isocyanate formed by this procedure was hydrolyzed readily to an oily 2-phenylcyclopropylamine which was characterized as the hydrochloride and benzoyl derivative. The yield of amine was 83%.

Since acid B furnishes the same chloride as its stereoisomer, it could obviously not be degraded to the amine of its own configuration by the same procedure. It was possible, however, to convert the methyl ester of acid B to a crystalline hydrazide which differed from the hydrazide of acid A prepared for comparison. Diazotization of the B-hydrazide, thermal rearrangement of the azide, and hydrolysis of the isocyanate led to a new 2-phenylcyclopropylamine, different from that obtained by Curtius degradation of acid A. The properties of the hydrochloride and benzoyl derivatives confirmed this difference.

N-(2-Phenylcyclopropyl)-benzamide A was treated with phosphorus pentoxide in boiling toluene in a reaction patterned on the Bischler–Napieralski synthesis. The base obtained from this reaction analyzed for 1-phenyl-3,4-dihydro-3,-4-cyclopropanoisoquinoline. It differed in its physical properties (m. p. 109.5–110°) from 1-phenyl-3-methylisoquinoline (m. p. 89–90°)[5] and 1-phenyl-4-methylisoquinoline [liquid, b. p. 210° (20 mm.)][6] which might have conceivably been formed by rearrangement.

Methyl-(2-phenylcyclopropyl)-amine was prepared from 2-phenylcyclopropylamine A by the Decker method,[7] and dimethyl-(2-phenylcyclopropyl)-amine by methylation of the primary amine with formaldehyde and formic acid.

The pharmacological action of the amines described in this article will be reported by Dr. E. J. Fellows of Temple University Medical School.

**Acknowledgment.**—We are grateful to Smith, Kline and French Laboratories for a generous grant which made this investigation possible.

## Experimental[8]

**Ethyl 2-Phenylcyclopropanecarboxylate.**—This ester was prepared by a modification of the directions of Buchner and Geronimus.[4] A solution containing 167 g. (1.61 moles) of stabilized styrene and 183 g. (1.61 moles) of

(5) Wolfes and Dobrowsky, German Patent 456,709 (1930); *Chem. Abstr.*, **27**, 310 (1933).

(6) Boedecker and Heymons, German Patent 674,400 (1939); *Chem. Abstr.*, **33**, 5004 (1939).

(7) Decker and Becker, *Ann.*, **395**, 366 (1913).

(8) All melting points are corrected. The microanalyses were performed by Clark Microanalytical Laboratories, Urbana, Illinois.

ethyl diazoacetate was cooled to 0° and dropped into 83.5 g. (0.803 mole) of styrene with stirring, in a dry nitrogen atmosphere, at 125–135°. The rate of addition was so adjusted that the exothermic reaction held the temperature without heating. After eight hours, the gas evolution stopped, and the pale reddish mixture was distilled. A low-boiling fraction consisting largely of unchanged styrene (41% of the total amount used) was separated, and the ester was collected. It boiled at 103–105° (0.5–0.7 mm.), 105–110° (1–2 mm.), or 131° (10 mm.). The yield was 208 g. (68% based on ethyl diazoacetate, 77% based on unrecovered styrene).

**2-Phenylcyclopropanecarboxylic Acid A.**—A solution of 207.8 g. of the ester and 64.5 g. of sodium hydroxide in 80 cc. of water and 600 cc. of ethanol was refluxed for nine hours, the alcohol was removed by distillation, and the residue was dissolved in water. The carboxylic acid was liberated with 200 cc. of concentrated hydrochloric acid. It precipitated as an oil which solidified soon, or directly as crystals which were filtered and washed with water. The amber solid was recrystallized from boiling water in which it is soluble to about 1%.

The cooled solution deposited 131.6 g. (74.5%) of colorless felted needles which melted, after further recrystallization, at 93°.

*Anal.* Calcd. for $C_{10}H_{10}O_2$: C, 74.05; H, 6.22; mol. weight, 162.2. Found: C, 74.24; H, 6.35; mol. weight, 161.8.

**2-Phenylcyclopropanecarboxylic Acid B.**—When the aqueous mother liquors from the recrystallization of the A-acid were concentrated and extracted with benzene, addition of low-boiling petroleum ether to the extract caused precipitation of compact crystals. The material weighed 12–13% of the calculated amount and melted, after recrystallization from boiling water, or benzene-petroleum ether, at 106–107°.

*Anal.* Calcd. for $C_{10}H_{10}O_2$: C, 74.05; H, 6.22; mol. wt., 162.2. Found: C, 74.27; H, 6.09; mol. wt., 161.7.

**2-Phenylcyclopropanecarbonyl Chloride.**—A solution of 4.62 g. (0.0285 mole) of 2-phenylcyclopropanecarboxylic acid A or B in 15 cc. of dry benzene was refluxed with 4 cc. (*ca.* 0.057 mole) of thionyl chloride for five hours, the volatile liquids were removed, and the residue once more distilled with benzene. Fractionation of the residue yielded 4.82 g. (93.6%) of a colorless oil boiling at 108–110° (2–2.1 mm.).

Hydrolysis of the acid chloride with cold water always furnished a quantitative yield of the pure A-acid, m. p. 93°.

**2-Phenylcyclopropanecarbonamide A.**—When the acid chloride just described was mixed with ice-cold 20% ammonium hydroxide, the amide formed in a yield of 81%. Recrystallized from boiling water, the pale brown platelets melted at 190–191°.

The mixture melting point of the amides obtained independently from the A- or B-acid *via* their common chloride showed no depression.

**2-Phenylcyclopropanecarboxylic Acid Hydrazide A.**—A solution of 0.9 g. of methyl 2-phenylcyclopropanecarboxylate A ($n^{27.5}D$ 1.5263, prepared from the acid with diazomethane in almost quantitative yield) and 15 cc. of 100% hydrazine hydrate in 2 cc. of absolute ethanol was refluxed gently for five hours, and most of the liquid removed under reduced pressure. The residue was dried in a vacuum desiccator over phosphorus pentoxide, and recrystallized from absolute ethanol with the aid of some dry ether. The yield of colorless crystals was 0.75 g. (84%), m. p. 127.5–129.5°.

*Anal.* Calcd. for $C_{10}H_{12}N_2O$: N, 15.90. Found: N, 15.97, 16.15.

**2-Phenylcyclopropylamine A.**—A three-necked flask was equipped with a mercury-sealed stirrer, a dropping funnel, and a reflux condenser, and the condenser was connected, through a drying tube, with an azotometer arranged to collect nitrogen over water. A mixture of 15 g. of *technical* sodium azide[9] and 50 cc. of dry toluene was stirred and warmed and a solution of 10 g. of 2-phenylcyclopropanecarbonyl chloride in 50 cc. of dry toluene was added slowly. Evolution of nitrogen began almost immediately and was essentially complete when the solvent began to boil. After forty minutes 96 to 98% of nitrogen had collected in the azotometer.

Inorganic salts were filtered and washed well with dry benzene, and the solvents were removed under reduced pressure. The residual isocyanate was a clear red oil of characteristic odor. It was cooled to 10°, and treated cautiously with 100 cc. of 35% hydrochloric acid in small portions with shaking. After most of the evolution of carbon dioxide had subsided the mixture was refluxed for thirteen hours, the cooled solution was diluted with 75 cc. of water and extracted with three 50-cc. portions of ether. The acid solution was evaporated under reduced pressure with occasional additions of toluene to reduce foaming.

The almost dry residue was cooled to 0°, and made strongly alkaline with a 50% potassium hydroxide solution. The amine was extracted into several portions of ether, dried over potassium hydroxide, the solvent was removed, and the base fractionated. The colorless mobile oil boiled at 69–71° (0.5 mm.), 74–81° (1.7 mm.), and weighed 6.15 g. (83%).

Conversion to the hydrochloride proceeded best in ethyl acetate–ether solution. Over-neutralization had to be avoided because of the formation of yellow decomposition products. The crude salt, obtained in a yield of 95%, was recrystallized by dissolving it in the least amount of cold methanol, and precipitating with absolute ethyl acetate and ether. The colorless needles thus obtained sintered at 151.5°, m. p. 153.5–156.5° (dec.).

*Anal.* Calcd. for $C_9H_{12}ClN$: C, 63.71; H, 7.13; N, 8.26; Cl, 20.90. Found: C, 63.55; H, 7.53; N, 8.13; Cl, 21.05.

The **benzoyl derivative** was prepared by a Schotten-Baumann reaction. The colorless crystals were recrystallized from absolute methanol, m. p. 122–123.5°.

*Anal.* Calcd. for $C_{16}H_{15}NO$: N, 5.90. Found: N, 6.03.

**2-Phenylcyclopropanecarboxylic Acid Hydrazide B.**—Methyl 2-phenylcyclopropanecarboxylate B was prepared from the acid with diazomethane in a yield of 92%. The oily ester showed $n^{29}D$ 1.5215. The hydrazide was obtained from the ester in the same manner as the A-isomer. The yield was 83.8%. The colorless crystals, collected from alcohol–ether, melted at 111–112°. The hydrochloride melted at 188–191°.

*Anal.* Calcd. for $C_{10}H_{13}ClN_2O$: N, 13.16. Found: N, 13.17.

The **isopropylidene derivative**, prepared from the hydrazide and acetone, melted at 166–166.5°.

*Anal.* Calcd. for $C_{13}H_{16}N_2O$: N, 12.95. Found: N, 13.18.

**2-Phenylcyclopropylamine B.**—To a stirred solution of 7.5 g. of the B-hydrazide in 70 cc. of water and 20 cc. of 35% hydrochloric acid, a solution of 3.6 g. of sodium nitrite in 10 cc. of ice water was added at −3° to +5°. A yellow oil precipitated from the mixture. After another ninety minutes at 0 to 5°, the mixture was extracted with four 30-cc. portions of ether, the combined extracts were dried over sodium sulfate, and the ether was removed at 20°. The light red residue was dissolved in toluene and decomposed by heating until the evolution of nitrogen ceased. The solvent was stripped under reduced pressure, the dark isocyanate hydrolyzed by refluxing with 25 cc. of 35% hydrochloric acid for five and one-half hours, and the acid was distilled *in vacuo*. The residue was made strongly alkaline with 40% potassium hydroxide solution at 0°, the liberated amine extracted into ether, and dried over potassium hydroxide. After removal of the ether, the colorless oil boiled at 79–80° (1.5–1.6 mm.). The yield was 2.5 g. (44%).

(9) From Fairmount Chemical Co., Newark, N. J.

The hydrochloride crystallized from ethyl acetate and ether. The colorless crystals melted at 164–166° (dec.).

*Anal.* Calcd. for $C_9H_{12}ClN$: C, 63.71; H, 7.13. Found: C, 63.62, 63.89; H, 7.13, 7.36.

A mixture melting point with the stereoisomeric hydrochloride (m. p. 153.5–156.5°) was 94–104° (dec.).

The benzoyl derivative crystallized from dilute ethanol, m. p. 119–120°.

*Anal.* Calcd. for $C_{16}H_{15}NO$: N, 5.90. Found: N, 6.07.

A mixture melting point with the A-benzoyl derivative (m. p. 122–123.5°) showed a 20–30° depression.

**(2-Phenylcyclopropyl)-dimethylamine.**—Following general directions[10] for the methylation of primary amines, 10.2 g. of a 40% aqueous formaldehyde solution was added to a cooled solution of 5 g. of 2-phenylcyclopropylamine A in 13.2 g. of 90% formic acid, and the mixture was refluxed overnight. The cooled reaction mixture was treated with 5.5 cc. of concentrated hydrochloric acid, the solution was evaporated under reduced pressure, the residue was made alkaline with a 50% potassium hydroxide solution, and the amine extracted into ether. After drying over potassium hydroxide and distillation of the ether, the colorless amine boiled at 70–70.5° (1.3–1.5 mm.).

The hydrochloride was prepared in dry ether solution and weighed 2.0 g. (27%). After recrystallization from ethyl acetate–ether, the colorless crystals showed m. p. 187–189° (dec.).

*Anal.* Calcd. for $C_{11}H_{16}ClN$: C, 66.82; H, 8.16. Found: C, 66.85, 66.93; H, 8.20, 8.22.

**(2-Phenylcyclopropyl)-methylamine.**—A solution of 5 g. of 2-phenylcyclopropylamine A and 4.3 g. of benzaldehyde in 10 cc. of absolute ethanol was refluxed for three hours, the solvent was stripped under reduced pressure, and the benzal derivative distilled once. The colorless oil boiled at 170–172° (2 mm.). It was not purified further. The yield was 6 g. (70%).

A mixture of 6 g. of (2-phenylcyclopropyl)-benzalamine and 7.7 g. of methyl iodide was heated in a sealed tube at 95° for seven hours. The dark red viscous reaction product was boiled with 75 cc. of 95% ethanol for four hours, the solvent was removed under reduced pressure, the base was liberated with 40% potassium hydroxide solution and extracted with ether. The extract was dried over potassium hydroxide, the ether evaporated, and the amine distilled. The colorless mobile distillate, obtained in a yield of 25%, boiled at 88–90° (1.5 mm.).

The colorless **hydrochloride** crystallized from ethanol–ether, m. p. 99–124.5°. Repeated recrystallizations did not narrow this melting point range.

*Anal.* Calcd. for $C_{10}H_{14}ClN$: N, 7.63. Found: N, 7.53.

**1-Phenyl-3,4-dihydro-3,4-cyclopropanoisoquinoline.**—A solution of 5 g. of N-(2-phenylcyclopropyl)-benzamide A in 100 cc. of dry toluene was refluxed with 5 g. of phosphorus pentoxide for twenty minutes. Another 5 g. of phosphorus pentoxide was added, and boiling was continued for forty minutes. The mixture was cooled, the toluene decanted, and the residue was decomposed with ice and slow warming until the ice was melted. The resulting solution was cleared, washed with ether, and made strongly alkaline with a 40% potassium hydroxide solution. The reaction product was extracted with four 75-cc. portions of benzene, and the solvent was evaporated. The oily residue solidified to pale brown prisms which were recrystallized from absolute ethanol. The yield was 21%, m. p. 109.5–110.5°.

*Anal.* Calcd. for $C_{16}H_{13}N$: C, 87.64; H, 5.97. Found: C, 88.17; H, 5.75.

The hydrochloride was hygroscopic. The **diliturate** consisted of yellow prisms which were recrystallized from water and melted at 137–140° with darkening, and decomposed at 156–161°.

*Anal.* Calcd. for $C_{20}H_{16}N_4O_5$: N, 14.28. Found: N, 14.04.


## Summary

Condensation of styrene with ethyl diazoacetate yields two stereoisomeric 2-phenylcyclopropanecarboxylic acids. The higher-melting member of this pair rearranges to the lower-melting one by way of their common chloride. Both acids have been degraded to the corresponding stereoisomeric 2-phenylcyclopropylamines by different modifications of the Curtius reaction. Secondary and tertiary amines in this series have been prepared, and the benzoyl derivative of the more readily accessible 2-phenylcyclopropylamine has been cyclized to a compound which probably is 1-phenyl-3,4-dihydro-3,4-cyclopropanoisoquinoline.


CHARLOTTESVILLE, VA. RECEIVED JANUARY 26, 1948

(10) Clarke, Gillespie and Weishaus, THIS JOURNAL, **55**, 4571 (1933).

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[CONTRIBUTION FROM THE CHEMISTRY LABORATORY, NATIONAL INSTITUTE OF HEALTH, U. S. PUBLIC HEALTH SERVICE]

# Methyl 2,6-Anhydro-α-D-altroside and Other New Derivatives of Methyl α-D-Altroside[1]

BY DAVID A. ROSENFELD, NELSON K. RICHTMYER AND C. S. HUDSON

In continuation of earlier researches in this Laboratory on methyl α-D-altroside,[2] we now wish to describe a number of new crystalline derivatives of this glycoside. Our primary objective was the study of 6-desoxy-D-altrose (D-altromethylose), the corresponding L-form having been obtained previously as a sirup by Freudenberg and Raschig.[3] From methyl α-D-altroside, following the general procedure described by Haskins, Hann and Hudson,[4] we were successful in preparing, in crystalline form, methyl 2,3,4-tribenzoyl-6-tosyl-α-D-altroside (I), methyl 2,3,4-tribenzoyl-6-iodo-6-desoxy-α-D-altroside (II), methyl 6-iodo-6-desoxy-α-D-altroside, and methyl 2,3,4-tribenzoyl-6-desoxy-α-D-altroside (III). However, our attempts to transform this last-named compound to the desired methyl 6-desoxy-α-D-altroside and to 6-desoxy-D-altrose have so far yielded only sirups. Gut and Prins[5] have also described these two com-

(1) Presented in part before the Division of Sugar Chemistry and Technology at the Atlantic City meeting of the American Chemical Society, April 14, 1947.

(2) N. K. Richtmyer and C. S. Hudson, THIS JOURNAL, **63**, 1727 (1941).

(3) K. Freudenberg and K. Raschig, *Ber.*, **62**, 373 (1929).

(4) W. T. Haskins, R. M. Hann and C. S. Hudson, THIS JOURNAL, **68**, 628 (1946).

(5) M. Gut and D. A. Prins, *Helv. Chim. Acta*, **29**, 1555 (1946).