7-Methyl-2,3,10,11-tetramethoxy-5,6,13,13a-tetrahydro-8-dibenzo(a,g)quinolizinium Iodide (VI).—This quaternary salt was obtained in essentially quantitative yield by refluxing a solution of 2 g. of 2,3,10,11-tetramethoxy-5,6,13,13a-tetrahydro-8-dibenzo(a,g)quinolizine and 1 cc. of methyl iodide in 50 cc. of benzene for three and one-half hours. The tiny white needles which precipitated melted at 244–249°.[21] No attempt was made to separate the diastereoisomers.

Anal. Calcd. for $C_{22}H_{28}INO_4$: C, 53.12; H, 5.67. Found: C, 52.75; H, 5.71.

1-Benzyl-1,2,3,4-tetrahydroisoquinoline.—A 20-g. sample of N-(β-phenylethyl)-phenylacetamide[22] was converted to 1-benzyl-3,4-dihydroisoquinoline by treatment with phosphorus pentoxide in boiling tetralin according to the procedure of Späth, Berger and Kuntara.[23] The light yellow oil (10 g., 54%) was dissolved in 75 cc. of ethanol, 1 g. of Raney nickel added, and the solution shaken for three hours at 70° under hydrogen at 3.5 atm. The catalyst was removed by filtration and the filtrate concentrated to about 40 cc. An excess of dry hydrogen chloride gas was introduced and ether added to facilitate precipitation. The 8.8 g. of colorless crystals obtained represent a 75% yield in the hydrogenation. A small sample after recrystallization from ethanol–ether melted at 172–173°.[24]

1-Benzyl-2-methyl-1,2,3,4-tetrahydroisoquinoline (VII).—The free base from 3.3 g. of 1-benzyl-1,2,3,4-tetrahydroisoquinoline hydrochloride was dissolved in 75 cc. of absolute ethanol and an excess of anhydrous formaldehyde introduced as above. About 0.5 g. of Raney nickel was added and the solution shaken for three hours at room temperature under hydrogen at 3.3 atm. The catalyst was removed by filtration and the ethanol removed by distillation, leaving 2.3 g. (66%) of very light yellow oil. The picrate was obtained as tiny yellow needles from ethanol, m. p. 166.5–167°.[25]

(21) Osada, *J. Pharm. Soc.*, No. 547, 711 (1927), reported a m. p. of 245°. Haworth, Koepfli and Perkin, *J. Chem. Soc.*, 2263 (1927), reported a m. p. of 266° for the β-isomer, 230° for the α-isomer. Robinson and Sugasawa, *ibid.*, 789 (1932), reported a m. p. of 215°.

(22) Prepared by the method of Decker, *Ann.*, **395**, 282 (1912).

(23) Späth, Berger and Kuntara, *Ber.*, **63**, 134 (1930).

(24) Leithe (ref. 10a) reported a m. p. of 173°.

(25) Forsyth, Kelly and Pyman (ref. 10b) reported a m. p. of 165–167°.

1-Benzyl-2,2-dimethyl-1,2,3,4-tetrahydroisoquinolinium Iodide (VIII).—A dry benzene solution (50 cc.) of 2.2 g. of 1-benzyl-2-methyl-1,2,2,4-tetrahydroisoquinoline and 2 cc. of methyl iodide was refluxed for three hours on a steam-bath. The light tan powder obtained on filtering the cooled reaction mixture amounted to 2.9 g. (83%). After recrystallization from absolute ethanol, 2.5 g. (72%) of tiny colorless needles were obtained, m. p. 242°.[26]

5,6,13,13a-Tetrahydro-8-dibenzo[a,g]quinolizine (IX).—Attempts to prepare 5,6,13,13a-tetrahydro-8-dibenzo-[a,g]quinolizine by treatment of 1-benzyl-1,2,3,4-tetrahydroisoquinoline with formaldehyde in the presence of hydrochloric acid, or of sodium bicarbonate, were unsuccessful. It was prepared in 38% yield by the method of Leithe,[11] m. p. of the free base 84–85°, m. p. of the hydrochloride 231–232°.

7-Methyl-5,6,13,13a-tetrahydro-8-dibenzo[a,g]quinolizinium Iodide (X).—A dry solution of 0.6 g. of 5,6,13,-13a-tetrahydro-8-dibenzo[a,g]quinolizine and 2 cc. of methyl iodide in 50 cc. of dry benzene was refluxed for four hours. The light tan precipitate which formed was collected by filtration and dried. The 0.8 g. of product after recrystallization from ethanol–ether with charcoal treatment gave 0.7 g. (73%) of very light tan powder, m. p. 198–202°.[27] No attempt was made to separate the diastereoisomers.

Anal. Calcd. for $C_{18}H_{20}IN$: C, 57.30; H, 5.34. Found: C, 57.64; H, 5.36.

Summary

1-Benzyltetrahydroisoquinolines have been synthesized by improved methods. Quaternary salts of these compounds exhibited curare-like activity, the most effective being 1/75th as active as *d*-tubocurarine chloride.

(26) Leithe (ref. 10a) reported a m. p. of 242°. Freund and Bode, *Ber.*, **42**, 1763 (1909), reported a m. p. of 239–242°.

(27) Chakravarti, Haworth and Perkin, *J. Chem. Soc.*, 2275 (1927), reported a m. p. of 230–232° for the β-isomer, 212° for the α-isomer.

ROCHESTER, N. Y. RECEIVED APRIL 17, 1948

[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF G. D. SEARLE AND CO.]

Synthesis of Some Iodo-sugar Derivatives[1]

BY ALBERT L. RAYMOND AND ELMER F. SCHROEDER

The use of iodinated organic compounds as X-ray contrast agents in urography has become well established in recent years. However, the administration of such compounds by the intravenous route is attended by an element of danger because of occasional side effects. In a search for other suitable contrast agents of lower toxicity, a number of water soluble iodo-sugar derivatives have been prepared and subjected to preliminary tests. These include 6-iodo-6-desoxy-D-galactose (I), 6-iodo-6-desoxy-α-methyl-D-glucopyranoside (II), 6-iodo-6-desoxy-β-methyl-D-glucopyranoside (III) and 6-iodo-6-desoxy-1,4-sorbitan (IV).

The introduction of the iodine atom into the sugar residues was accomplished by the well-known procedure of Oldham and Rutherford[1a] by heating the corresponding 6-*p*-toluenesulfonyl (tosyl) derivative, suitably stabilized by substituent groups, with sodium iodide in acetone solution. Thus, 6-iodo-6-desoxy-D-galactose was obtained by the following series of reactions: 1,2,3,4-diisopropylidene-D-galactose[2] → 6-tosyl-1,2,3,4-diisopropylidene-D-galactose[3] → 6-iodo-6-desoxy-1,2,3,4-diisopropylidene-D-galactose[4] → 6-iodo-6-desoxy-D-galactose. The final step in this series was carried out by hydrolysis of the diisopropyli-

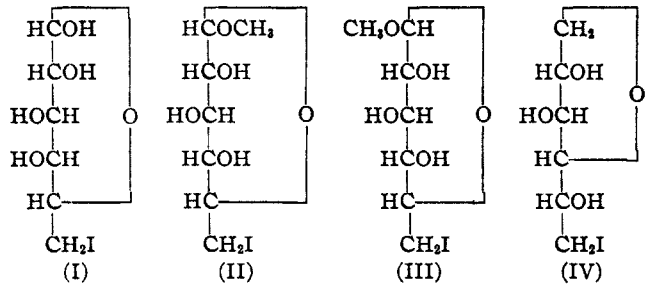
(1) Presented before the Division of Sugar Chemistry and Technology of the American Chemical Society at the Chicago meeting, April, 1948.

(1a) Oldham and Rutherford, THIS JOURNAL, **54**, 366 (1932).

(2) Van Grunenberg, Bredt and Freudenberg, *ibid.*, **60**, 1507 (1938).

(3) Freudenberg and Hixon, *Ber.*, **56**, 2119 (1923).

(4) Freudenberg and Raschig, *ibid.*, **60**, 1633 (1927).



dene derivative in 50% acetic acid. The iodogalactose was readily obtained in crystalline form by treatment with absolute ethanol, from which it separated in rectangular plates containing one molecule of ethanol. The anhydrous form resulted on recrystallization of the alcoholate from an acetic acid–methyl ethyl ketone mixture. It melted at 114–116° and rotated $[\alpha]^{25}D$ + 75.3° (three minutes) in water, decreasing to a constant $[\alpha]^{25}D$ + 66.9° in about five hours. The anhydrous form readily gave crystalline alcoholates also with methanol and 2-propanol. On treatment with phenylhydrazine, an insoluble phenylhydrazone was precipitated at room temperature.

6-Iodo-6-desoxy-α-methyl-D-glucopyranoside was recently prepared by Zief and Hockett[5] by deacetylation of 6-iodo-6-desoxy-2,3,4-triacetyl-α-methyl-D-glucopyranoside with hot aqueous–alcoholic hydrogen chloride. We obtained the same compound simply by treating α-methyl-D-glucopyranoside in pyridine with one mole of tosyl chloride, and after removal of the pyridine, heating the sirupy reaction product with sodium iodide in acetone solution. From the resulting digest, the iodo-glucoside was isolated directly in about 22% yield. Alternatively, the crude product from the iodide digestion may be converted by acetylation into 6-iodo-6-desoxy-2,3,4-triacetyl-α-methyl-D-glucopyranoside, which can then be catalytically deacetylated by means of sodium methoxide in methanol solution.[6] The fact that this deacetylation can be smoothly and practically quantitatively accomplished by no more than about 0.01 mole equivalent of sodium methoxide is rather surprising in view of the presence of the halogen atom. The 6-iodo-6-desoxy-α-methyl-D-glucopyranoside obtained by either procedure, after recrystallization from ethanol, melted at 146–147°, and rotated $[\alpha]^{25}D$ + 101.5° in water.

6-Iodo-6-desoxy-β-methyl-D-glucopyranoside was obtained in similar manner, by treatment of β-methyl-D-glucopyranoside hemihydrate with 1.5 mole equivalents of tosyl chloride in pyridine. However, in this case, when the sirupy tosylation product was heated with sodium iodide in acetone, the iodo-glucoside, which itself is easily soluble in warm acetone, separated from the hot reaction mixture presumably as an insoluble complex with sodium *p*-toluenesulfonate. This complex is probably analogous to those described by Watters, Hockett and Hudson[7] of certain β-methyl glycosides with potassium acetate. Treatment of the complex with an acetylating mixture yielded 6-iodo-6-desoxy-2,3,4-triacetyl-β-methyl-D-glucopyranoside, which on deacetylation with sodium methoxide gave the desired 6-iodo-6-desoxy-β-methyl-D-glucopyranoside in an over-all yield of 53%. The product separated from alcohol as needles melting at 157–158° and rotating $[\alpha]^{25}D$ −17° in water.

The synthesis of 6-iodo-6-desoxy-1,4-sorbitan, and several of its derivatives, is represented schematically. On treatment of 1,4-sorbitan (V) with tosyl chloride at low temperature, a 53% yield of 6-tosyl-1,4-sorbitan (VI) was obtained. This was condensed with benzaldehyde in the presence of hydrochloric acid or zinc chloride to give an excellent yield of 6-tosyl-2(3),5-benzylidene-1,4-sorbitan (VII), melting at 129.5–130.5° and rotating $[\alpha]^{25}D$ + 8.9° in water. As an alternative procedure, 1,4-sorbitan was condensed with benzaldehyde using zinc chloride as catalyst to give 2(3),5-benzylidene-1,4-sorbitan (VIII), melting at 154.5–155.5° and rotating $[\alpha]^{25}D$ + 17.7° in methanol,[8] which with tosyl chloride was converted almost quantitatively into 6-tosyl-2(3),5-benzylidene-1,4-sorbitan (VII) identical with the product obtained by benzalation of 6-tosyl-1,4-sorbitan. Treatment of the tosyl derivative with sodium iodide yielded 6-iodo-6-desoxy-2(3),5-benzylidene-1,4-sorbitan (IX) which was readily hydrolyzed by heating for ten minutes at 100° in aqueous–alcoholic 0.1 *N* sulfuric acid to give an 85% yield of 6-iodo-6-desoxy-1,4-sorbitan (IV), melting at 108–109° and rotating $[\alpha]^{25}D$ − 11.9° in water.

The assignment of the tosyl group, and consequently of the iodine atom, to the 6 position in these compounds follows from the Oldham–Rutherford rule[1a] that only tosyl groups attached to primary alcohol groups are readily replaceable by iodine on treatment with sodium iodide. The location of the benzylidene group has not been completely established. However, that one of the linkages is attached to position 5 is highly probable in view of the observation that, while 6-tosyl-1,4-sorbitan (VI) on treatment with sodium iodide decomposes with liberation of iodine, its benzylidene derivative (VII) reacts smoothly without evidence of decomposition. In our experience,[9] when 6-tosyl derivatives, having an unprotected secondary hydroxyl group in the adja-

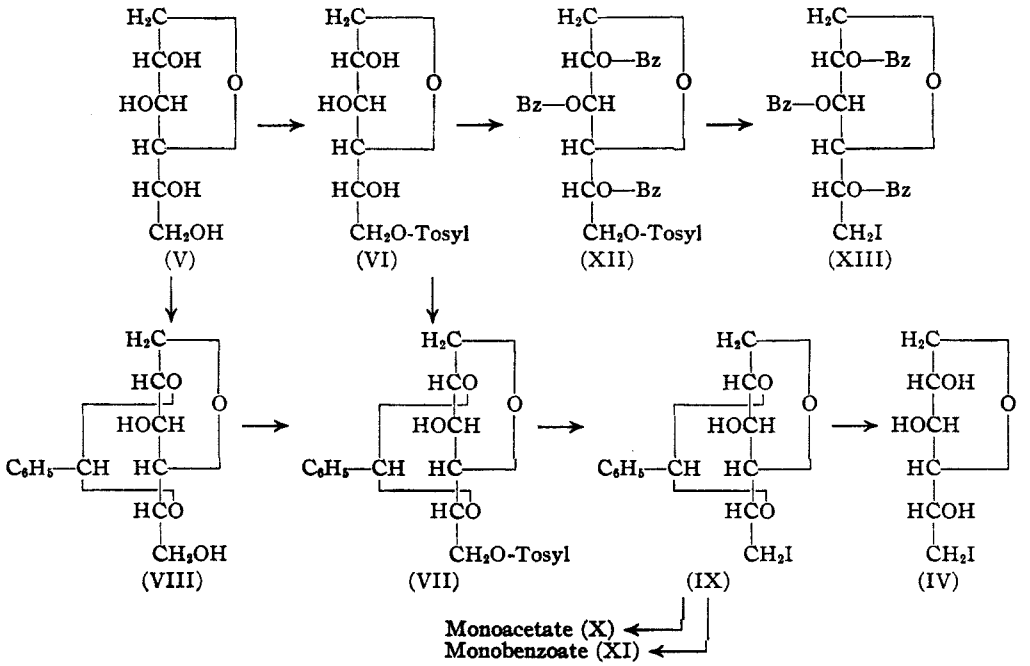
(5) Zief and Hockett, THIS JOURNAL, **67**, 1267 (1945).

(6) Zemplén and Pacsu, *Ber.*, **62**, 1613 (1929).

(7) Watters, Hockett and Hudson, THIS JOURNAL, **56**, 2199 (1934).

(8) Soltzberg, Goepp and Freudenberg, *ibid.*, **68**, 919 (1946), recently reported the preparation in small yield of two additional monobenzylidene-1,4-sorbitans by refluxing sorbitan with benzaldehyde without catalyst. That neither of these is identical with the product obtained by us is indicated by the reported constants (m. p. 136–140°, $[\alpha]D$ +33.72° in methanol for the first and m. p. 121–122° for the second).

(9) Unpublished results. See also Bell, Friedmann and Williamson, *J. Chem. Soc.*, 252 (1937).



cent 5 position, are heated with sodium iodide there is a greater or less tendency for liberation of free iodine to occur. This is not evident when the 5 position is blocked, either by a substituent group or, as in the case of the 6-tosyl-α- and β-methyl-D-glucopyranosides, by the presence of a pyranoid ring structure.

Several additional derivatives of 1,4-sorbitan were prepared during the course of this work. 6-Iodo-6-desoxy-2(3),5-benzylidene-1,4-sorbitan (IX) gave a monoacetate (X) and a monobenzoate (XI). On treatment of crystalline 6-tosyl-1,4-sorbitan (VI) with excess benzoyl chloride, there was obtained 6-tosyl-2,3,5-tribenzoyl-1,4-sorbitan (XII) melting 106–107° and rotating $[\alpha]^{25}D$ +47.2° in chloroform,[10] converted by sodium iodide into 6-iodo-6-desoxy-2,3,5-tribenzoyl-1,4-sorbitan (XIII). The latter could not be debenzoylated without simultaneous loss of iodine.

The iodo-sugar derivatives (I-IV) are readily soluble in water to give colorless solutions. Thus 6-iodo-6-desoxy-D-galactose (I) and 6-iodo-6-desoxy-1,4-sorbitan (IV) dissolve at room temperature in their own weight of water. The two 6-iodomethyl-D-glucopyranosides are less soluble, dissolving in about two parts of water at 50°, but partially crystallizing out again on cooling. The β-form separates from water in needles, while the α-form produces rods frequently several centimeters long.

These compounds show a wide divergence in the firmness with which the iodine atom is held, as is shown in Table I. These data were obtained by dissolving equivalent amounts of the iodo-sugar derivatives (0.0013 mole) in 25 cc. of water, immersing for exactly thirty minutes in a boiling water-bath, then titrating the hydrogen iodide formed with standard alkali.

TABLE I

STABILITY OF IODO-SUGAR DERIVATIVES AT 100°

Compound	Cc. 0.01 *N* NaOH required	% Decomposition
I	2.20	1.66
II	0.10	0.07
III	0.18	0.13
IV	44.80	33.7

As would be expected, the stabilizing effect of the pyranoid ring is evident. The two iodomethyl-D-glucopyranosides (II and III), having a fixed ring structure, show only negligible decomposition; iodo-D-galactose (I), in which a ring shift is possible in solution, is somewhat less stable, while iodo-sorbitan (IV), having a free hydroxyl group adjacent to the iodine, is by far the least stable. At room temperature, aqueous solutions of the iodo-D-glucosides remain unchanged indefinitely, while solutions of iodo-D-galactose and iodo-sorbitan show evidence of acid liberation within several months and several weeks, respectively.

Pharmacological studies carried out on dogs have shown that 6-iodo-6-desoxy-D-galactose exhibits a fairly low acute toxicity, is concentrated rapidly by the kidneys, and yields satisfactory X-ray pictures of the kidney region. However, in view of the relatively low stability of the carbon–iodine linkage, the application to clinical use must await further study.

(10) After completion of our experimental work on this compound, Hockett, Conley, Yusem and Mason, THIS JOURNAL, **68**, 922 (1946), reported its preparation directly from 1,4-sorbitan without isolation of the intermediate 6-tosyl-1,4-sorbitan. However, the constants reported by these investigators are at considerable variance with those found by us (m. p. 161.5–163.0°, rotation +35.1° in chloroform).

Experimental

1,2,3,4-Diisopropylidene-D-galactose.—Crude diisopropylidene galactose was prepared by a modification of the method of Gruenenberg, Bredt and Freudenberg.[2] The principal changes introduced were in the substitution of sulfuric acid for the phosphoric acid–phosphorus pentoxide catalyst, and in a considerable reduction in the quantity of acetone used.

A mixture consisting of anhydrous D-galactose (200 g.), acetone (2500 cc.), powdered, fused zinc chloride (240 g.), and sulfuric acid (8 cc.), was stirred for four hours at room temperature. The reaction mixture was treated with a solution of 400 g. of sodium carbonate in 700 cc. of water, and vigorously stirred until the supernatant liquid became zinc-free. The precipitated salts were filtered off and washed with acetone. The filtrate, consisting of two liquid phases, was completely freed of acetone by distillation, and the crude diisopropylidene galactose, separating as a light-yellow upper layer, was taken up in ether, washed with water, and dried with sodium sulfate. After removal of the solvent, the yield of crude product was 260 g., or 90% of theory.

6-Tosyl-1,2,3,4-diisopropylidene-D-galactose.—The procedure of Freudenberg and Hixon[2] was somewhat modified for this preparation. A solution of 260 g. (1 mole) of crude diisopropylidene galactose in a mixture of 275 cc. of acetone and 175 cc. of pyridine was cooled in tap water. With stirring, 228 g. (1.2 moles) of tosyl chloride was added in portions over a period of one hour, the temperature being maintained below 45°. After standing overnight, the excess tosyl chloride was decomposed by the addition of 10 cc. of water. The reaction mixture was then poured into 2.5 liters of water, a sirupy product precipitating, which solidified on standing for several hours. This was filtered off, washed with water, and air-dried; yield, 360 g. The product was dissolved in 360 cc. of 2-propanol, and allowed to crystallize overnight at room temperature. After 360 cc. of Skellysolve C were gradually added with stirring, the crystals were filtered off and washed with Skellysolve C. The yield was 275 g. (66%) of product melting at 87–89°; reported,[3] 91–92°. If the product melts much below this point, it must be recrystallized before use in the subsequent reaction with sodium iodide.

6-Iodo-6-desoxy-1,2,3,4-diisopropylidene-D-galactose.—The procedure of Freudenberg and Raschig[4] was somewhat modified for this preparation. A solution of 248 g. (0.6 mole) of 6-tosyl-1,2,3,4-diisopropylidene-D-galactose and 180 g. (1.2 moles) of sodium iodide in 1250 cc. of acetone was heated at 105–110° for thirty-six hours.[11] After removal of the precipitated sodium *p*-toluenesulfonate by filtration and washing with acetone, the filtrate was concentrated under reduced pressure. The residual sirup was stirred with 1 liter of water and a few crystals of sodium thiosulfate to destroy traces of free iodine. After several hours, the product solidified and was washed repeatedly with water. This crude material may be used directly, without drying, in the subsequent hydrolysis. If desired, it may be recrystallized from 250 cc. of methanol; yield, 190 g. (85%), melting at 69–71°; reported, 72°.[4]

6-Iodo-6-desoxy-D-galactose.—6-Iodo-6-desoxy-1,2,3,4-diisopropylidene-D-galactose (275 g.) was dissolved in 800 cc. of glacial acetic acid, immersed in a boiling water-bath, and with frequent shaking, treated with 750 cc. of hot water added in 50-cc. portions over a period of one hour. Heating was continued for one hour longer, at which time hydrolysis was complete as shown by the fact that a 1-cc. test portion remained clear on dilution with 5 cc. of water. In some runs, an additional twenty or thirty minutes of heating was required to complete hydrolysis. The solution was cooled, treated briefly with Darco, and filtered through a layer of Celite. The filtrate was then concentrated to a thin sirup under reduced pressure at a temperature not exceeding 40°. Absolute ethanol (500 cc.) was added, and the solution again concentrated. On redissolving the sirupy residue again in 800 cc. of absolute ethanol, cooling and scratching, a voluminous mass of crystals rapidly separated. After standing in the cold overnight, the product was filtered off, washed with ethanol, and twice recrystallized from 1500 cc. of absolute ethanol. The 6-iodo-6-desoxy-D-galactose prepared in this manner crystallized with one molecule of ethanol. The yield of alcoholate was 196 g., or 78% of the theoretical; rectangular plates, melting at 105–106° (cor.); very soluble in water, moderately soluble in hot alcohol, ethyl acetate and acetone, insoluble in chloroform and benzene. The substance had an initial (three minutes) rotation of $[\alpha]^{25}D$ +84.7° (*c*, 6.08 in water), which decreased to a constant value of +57.6° in five hours. Calculated on the basis of the iodo-galactose content, the latter becomes $[\alpha]^{25}D$ +66.8° (*c*, 5.24), identical with the constant value later obtained for anhydrous iodogalactose itself.

Anal. Calcd. for $C_6H_{11}O_5I \cdot C_2H_5OH$: C, 28.58; H, 5.10; I, 37.76. Found: C, 28.30; H, 4.86; I, 37.75, 38.0.

The alcohol is held quite tenaciously, being only incompletely removed by heating at 61° for seventeen hours (1 mm.). Calcd.: C_2H_5OH, 13.71. Found: C_2H_5OH, 12.2. Attempts to obtain the anhydrous form of the iodo-galactose by recrystallization from ethanol under a variety of conditions of concentration and temperature resulted in recovery of the starting material. The following procedure, however, gave the anhydrous form in good yield. A quantity of 50 g. of the alcoholate was heated for five minutes in a boiling water-bath with 25 cc. of glacial acetic acid. To the hot solution was added 250 cc. of hot, freshly distilled, methyl ethyl ketone. On cooling, anhydrous 6-iodo-6-desoxy-D-galactose separated in the form of needles, which were filtered off and washed with methyl ethyl ketone. The yield was 35 g. of product melting sharply at 113–114° (cor.), and rotating $[\alpha]^{25}D$ +75.3° (three minutes, *c*, 5.68 in water), decreasing to a constant value of +66.9° in about five hours.

Anal. Calcd. for $C_6H_{11}O_5I$: C, 24.84; H, 3.82; I, 43.75. Found: C, 24.78, 24.51; H, 3.82, 3.78; I, 43.87, 43.70.

Phenylhydrazone of 6-Iodo-6-desoxy-D-galactose.—To a solution of 7 g. of phenylhydrazine in 75 cc. of 50% acetic acid were added 3 g. of 6-iodo-6-desoxy-D-galactose. A white precipitate began to form at once. After one hour at room temperature the product was filtered off, washed with water and cold alcohol, and dried; yield 3.8 g.; theory, 3.93 g. After two recrystallizations from 120 cc. of 95% ethanol, the product darkened at 126° and melted with vigorous decomposition at 136–137° (cor.); $[\alpha]^{25}D$ +34.3° (*c*, 5.40 in pyridine), showing no evidence of mutarotation, but developing a marked yellow color in the pyridine solution in thirty minutes; rectangular plates.

Anal. Calcd. for $C_{12}H_{17}O_4N_2I$: N, 7.37; I; 33.42. Found: N, 6.99, 7.01; I, 33.49.

6-Iodo-6-desoxy-α-methyl-D-glucopyranoside.—A solution of 300 g. (1.55 moles) of α-methyl-D-glucopyranoside in 1500 cc. of dry pyridine was cooled in tap water and treated by the portionwise addition of 318 g. (1.67 moles) of tosyl chloride, the temperature being held below 40°. After standing for one hour longer, most of the pyridine was removed by distillation under reduced pressure. The residual sirup was taken up in 300 cc. of warm water, cooled, and neutralized (brom thymol blue) by the addition of 5 *N* sodium hydroxide (360 cc. required). The solution was concentrated to dryness under reduced pressure, and the residual sirup (700 g.) dissolved in 1200 cc. of acetone, some insoluble products being removed by filtration. Sodium iodide (210 g.) was dissolved in the acetone solution, which was transferred to pressure flasks and heated for two hours at 100°. Sodium *p*-toluene-

(11) Freudenberg and Raschig[4] employed a temperature of 125° for thirty-six hours. In our hands, considerable decomposition occurred under these conditions. At 105–110° the reaction is complete in thirty-six hours, as indicated by the practically quantitative yield of sodium *p*-toluene-sulfonate.

sulfonate was removed by filtration, washed with acetone, and the filtrate concentrated to dryness. The sirupy residue was dissolved in 700 cc. of water, extracted several times with dichloromethane and the aqueous phase then concentrated under reduced pressure. When about 500 cc. of distillate had been collected, the desired product began to separate out, and crystallization was complete after standing for twenty-four hours in the cold. The product was filtered off and recrystallized twice from 100 cc. of 95% ethanol; yield, 100 g., 22%.

Anal. Calcd. for $C_7H_{13}O_5I$: C, 27.65; H, 4.31; I, 41.74. Found: C, 27.72, 27.94; H, 4.40, 4.61; I, 41.71, 41.62.

The 6-iodo-6-desoxy-α-methyl-D-glucopyranoside is obtained as long rods melting sharply at 146–147° (cor.) and rotating $[\alpha]^{25}D$ +101.5° (*c*, 5.00 in water). Zief and Hockett[5] found m. p. 136.9–137.4° and $[\alpha]D$ +93.9° in water. The product is readily soluble in water but crystallizes out of concentrated aqueous solution on cooling, easily soluble in warm alcohol and acetone, insoluble in chloroform and benzene.

As an alternative procedure, we found that if, as sometimes occurred, the 6-iodo-glucoside failed to crystallize in the final distillation previously described, the residue could be taken to complete dryness and acetylated by addition of 500 cc. of pyridine and 500 cc. of acetic anhydride. On treatment with much water, 6-iodo-6-desoxy-2,3,4-triacetyl-α-methyl-D-glucopyranoside separated. Recrystallization from 900 cc. of 95% ethanol yielded 165 g. of pure product melting at 149–150°; reported,[12] 150–151°. Deacetylation was conveniently carried out by suspending this material in 375 cc. of methanol, adding 40 cc. of 0.1 *N* sodium methoxide in methanol, and shaking for one hour. On concentrating to dryness, the 6-iodo-6-desoxy-α-methyl-D-glucopyranoside separated as a solid mass and was recrystallized from 125 cc. of 95% ethanol; yield, 100 g.; m. p. 146–147°. A mixed melting point with the product obtained by direct isolation showed no depression.

Preparation of β-Methyl-D-glucopyranoside *via* its Potassium Acetate Complex.—Watters, Hockett and Hudson[7] reported that certain β-methyl-D-glycosides form molecular complexes with potassium acetate, and suggested that this property might be useful in some cases in the separation of the α- and β-isomers. We have found that this method offers a fairly convenient means of preparing β-methyl-D-glucopyranoside in quantity directly from D-glucose.

Anhydrous glucose (500 g.) was added to 1000 g. of methanol containing 3% by weight of hydrogen chloride, previously heated to a boil in a flask fitted with a reflux condenser and a calcium chloride tube. With occasional shaking, the heating was continued for just one hour. The solution was cooled, seeded with α-methyl-D-glucopyranoside, and allowed to stand in the icebox overnight. The α-methyl-glucopyranoside (90 g.) was filtered off and the filtrate neutralized by addition of 80 g. of solid sodium bicarbonate. After removal of the salts, the filtrate was concentrated to a thick sirup under reduced pressure. The sirup was dissolved in 500 cc. of hot absolute ethanol, treated with a hot solution of 200 g. of potassium acetate in one liter of ethanol, and allowed to stand overnight in the cold. The voluminous precipitate consisting mainly of the addition complex between β-methyl-D-glucopyranoside and potassium acetate, was filtered off, washed with ethanol and acetone, and finally dried briefly by heating at 100° under reduced pressure; yield, 200 g.

To decompose the complex, the 200 g. of crude addition complex was dissolved in 600 cc. of hot methanol and treated with a hot solution of 110 g. of D-tartaric acid in 600 cc. of 95% ethanol. After one hour the precipitated potassium acid tartrate was filtered off through Celite, the filtrate concentrated to a thin sirup (230 cc.), seeded, and allowed to stand in the cold to complete crystallization. The β-methyl-D-glucopyranoside separating was recrystallized from 500 cc. of 95% ethanol; yield, 115 g., or 21%, melting at 104–106° (cor.), and rotating $[\alpha]^{25}D$ −32° (*c*, 5.72 in water). The product was obtained as the hemihydrate.[13]

6-Iodo-6-desoxy-β-methyl-D-glucopyranoside.—A solution of 100 g. (0.51 mole) of β-methyl-D-glucopyranoside hemihydrate in 100 cc. of dry pyridine was cooled in running tap water and treated by the dropwise addition of a solution of 146 g. (0.76 mole) of tosyl chloride in 100 cc. of dichloromethane. The addition required about thirty minutes, the temperature being held below 45°. After one hour, the reaction mixture was neutralized by the addition of sodium hydroxide (required, 200 cc. of 5.17 *N* solution), using brom thymol blue as external indicator. The solution was concentrated to dryness under reduced pressure, the temperature being raised to 100° toward the end of the distillation to remove water as completely as possible. The sirupy residue (295 g.), together with 100 g. of sodium iodide, was dissolved in 400 cc. of acetone and heated for two hours at 100° in pressure flasks. The voluminous precipitate was filtered off, washed with acetone and air dried. It weighed 285 g. and consisted of some sodium chloride and sodium *p*-toluenesulfonate, together with a large amount of what is, probably, an insoluble complex between sodium *p*-toluenesulfonate and 6-iodo-6-desoxy-β-methyl-D-glucopyranoside.

To break up the complex[14] the 285 g. of material was covered with 150 cc. of dry pyridine and 150 cc. of acetic anhydride. After standing overnight at room temperature, the mixture was poured into two liters of water. After a short time the precipitated 6-iodo-6-desoxy-2,3,4-triacetyl-β-methyl-D-glucopyranoside was filtered off, washed with water, and recrystallized from 150 cc. of 95% ethanol. The yield was 129 g. (59%) of product melting at 114–115°; reported[15] m. p., 114–115°.

Deacetylation was carried out by suspending the 129 g. of triacetate in 300 cc. of methanol, adding 30 cc. of 0.1 *N* sodium methoxide solution, and shaking occasionally for about one hour. The solution was concentrated to dryness under reduced pressure, the 6-iodo-6-desoxy-β-methyl-D-glucopyranoside separating out near the end of the distillation in practically quantitative yield. It was twice recrystallized from 250 cc. of 95% ethanol, giving 82 g. (90%) of pure product. It separated in the form of long colorless needles melting at 157–158° (cor.) with decomposition, and rotating $[\alpha]^{25}D$ −17° (*c*, 5.00 in water). It is readily soluble in warm water, but crystallizes from a concentrated (40%) aqueous solution on cooling; readily soluble in warm alcohol and acetone, insoluble in chloroform.

Anal. Calcd. for $C_7H_{13}O_5I$: C, 27.65; H, 4.31; I, 41.74. Found: C, 27.99, 27.76; H, 4.49, 4.57; I, 41.67, 41.91.

6-Tosyl-1,4-sorbitan.—A solution of 200 g. (1.22 moles) of 1,4-sorbitan[16] in 800 cc. of pyridine was cooled to −5° and treated during one hour with 232 g. (1.22 moles) of tosyl chloride. After standing for two hours, most of the pyridine was removed by distillation under reduced pressure. The sirupy residue (660 g.) was taken up in 800 cc. of 95% ethanol, cooled to −5°, and neutralized with a cold 4 *N* solution of sodium hydroxide in 50% ethanol, using brom thymol blue as internal indicator (required 322 cc., theory 304). The precipitated sodium chloride was filtered off, and the filtrate concentrated to dryness under reduced pressure, the bath temperature not exceeding 50°. The sirupy residue (520 g.) was dis-

(12) Helferich and Himmen, *Ber.*, **61**, 1825 (1928).

(13) Koenigs and Knorr, *ibid.*, **34**, 957 (1901).

(14) Because of contamination with excess sodium *p*-toluenesulfonate, it was not possible to obtain the complex in sufficient purity for analysis. However evidence for its existence is seen in the fact that although 6-iodo-6-desoxy-β-methyl-D-glucopyranoside itself is readily soluble in warm acetone, it does precipitate from the hot acetone during the course of the sodium iodide reaction.

(15) Compton, THIS JOURNAL, **60**, 395 (1938).

(16) To this monoanhydride of sorbitol, a product of the Atlas Powder Co., has recently been assigned the trivial name Arlitan by Soltzberg, Goepp and Freudenberg.[6]

solved, with vigorous shaking, in 200 cc. of dichloromethane. On addition of 800 cc. more of this solvent, and cooling, the 6-tosyl-1,4-sorbitan crystallized out as a voluminous, pasty mass. A further 700 cc. of dichloromethane was added to aid in the crystallization, and after standing in the cold for several hours, the material was filtered off and air dried (300 g.). After two recrystallizations from an equal weight of warm water, 207 g. (53%) of product were obtained; rods, melting at 110–111° (cor.) and rotating $[\alpha]^{25}D$ −3.2 (*c*, 4.96 in water); readily soluble in alcohol and acetone, insoluble in ether, petroleum ether, or chloroform. The product may also be recrystallized with little loss from about twelve parts of ethylene dichloride.

Anal. Calcd. for $C_{13}H_{18}O_7S$: C, 49.05; H, 5.70; S, 10.07. Found: C, 49.1, 48.9; H, 5.68, 5.71; S, 10.23.

The same product was also obtained directly from D-sorbitol by treating a pyridine solution of the latter with two molecular equivalents of tosyl chloride, and neutralizing the reaction mixture as previously described. The amount of alkali required to reach the brom thymol blue end-point indicated that one of the tosyl groups of the 1,6-ditosyl-sorbitol presumably formed in the tosylation had been hydrolyzed during the neutralization. By working up the mixture as indicated above, 6-tosyl-1,4-sorbitan was isolated in a yield of 15%.

2(3),5-Benzylidene-1,4-sorbitan.—A mixture of 400 cc. of benzaldehyde, 100 g. of 1,4-sorbitan, and 100 g. of powdered fused zinc chloride was stirred for four hours. The temperature rose to 40°, and nearly complete solution occurred in one hour. After standing overnight the reaction mixture was repeatedly washed with water and Skellysolve C. The residual sirup was dissolved in a small amount of ethanol, treated with 100 cc. of toluene and evaporated to dryness under reduced pressure. The semi-solid mass was covered with more toluene and allowed to stand overnight in the cold. The crystalline material was filtered off and recrystallized from twelve parts of ethyl acetate. The product separated as rods, melting at 154.5–155.5° (cor.), and rotating $[\alpha]^{25}D$ +17.7° (*c*, 4.52 in methyl alcohol). The yield was 32 g.; readily soluble in acetone and alcohol, insoluble in ether, chloroform and benzene.

Anal. Calcd. for $C_{13}H_{16}O_5$: C, 61.89; H, 6.39. Found: C, 61.8, 61.9; H, 6.32, 6.22.

6-Tosyl-2(3),5-benzylidene-1,4-sorbitan. A. From 2(3),5-Benzylidene-1,4-sorbitan.—A solution of 10 g. (0.04 mole) of 2(3),5-benzylidene-1,4-sorbitan in 50 cc. of pyridine was cooled to −5°, and treated in small portions with 8.5 g. (0.044 mole) of tosyl chloride. After several hours at room temperature, the excess tosyl chloride was decomposed by addition of 2 cc. of water. On pouring the reaction mixture into 200 cc. of water, the product crystallized out at once; yield of crude product, 14 g., or 87%. After two recrystallizations from 8 parts of methanol, the material was obtained as needles melting at 129.5–130.5° (cor.), and rotating $[\alpha]^{25}D$ +8.9° (*c*, 5.88 in chloroform); insoluble in petroleum ether, readily soluble in acetone, ethyl acetate and chloroform.

Anal. Calcd. for $C_{20}H_{22}O_7S$: C, 59.10; H, 5.46; S, 7.89. Found: C, 59.1, 59.1; H, 5.36, 5.49; S, 8.24.

B. From 6-Tosyl-1,4-sorbitan.—A mixture of 100 g. of 6-tosyl-1,4-sorbitan, 100 cc. of water, 100 cc. of benzaldehyde, and 40 cc. of hydrochloric acid (sp. gr. 1.18) was vigorously stirred at room temperature for three hours. A crystalline precipitate began to form in about an hour. After standing overnight, the supernatant liquid was decanted, and the semi-solid residue shaken with 100 cc. of water and 300 cc. of Skellysolve C. The product was filtered off, suspended for a short time in dilute bicarbonate solution, then again filtered and washed with water and Skellysolve C. The crude yield was 116 g., or 91%. The crude material was dissolved in 1200 cc. of hot methanol in the presence of 2 g. of powdered calcium carbonate, and filtered. On cooling, 104 g. of pure material, melting at 129.5–130.5°, was obtained. A mixed melting point with the product prepared by method A showed no depression.

The same product was prepared in equally high yield, but less conveniently, by stirring a mixture of 100 g. of 6-tosyl-1,4-sorbitan, 400 cc. of benzaldehyde, and 100 g. of zinc chloride for four hours at room temperature, and isolating the product essentially as described previously.

6-Iodo-6-desoxy-2(3),5-benzylidene-1,4-sorbitan.—A solution of 40 g. (0.1 mole) of 6-tosyl-2(3),5-benzylidene-1,4-sorbitan and 30 g. (0.2 mole) of sodium iodide in 250 cc. of acetone was heated for two hours at 100° in a pressure flask. The precipitated sodium *p*-toluenesulfonate was removed by filtration, washed with acetone, and the colorless filtrate evaporated to a sirup under reduced pressure. On addition of water, the product crystallized immediately. After two recrystallizations from 5 parts of 95% ethanol, 28.5 g. (80%) of product was obtained; needles, melting at 147–148° (cor.), and rotating $[\alpha]^{25}D$ +24.8° (*c*, 4.00 in chloroform). The substance is insoluble in water and petroleum ether, moderately soluble in alcohol and benzene, and very soluble in acetone, ether, ethyl acetate and chloroform.

Anal. Calcd. for $C_{13}H_{15}O_4I$: C, 43.11; H, 4.17; I, 35.04. Found: C, 42.8, 43.0; H, 4.02, 4.12; I, 35.10.

It is essential that the tosyl-benzylidene-sorbitan used in the reaction with sodium iodide be quite pure. If it is not, extensive decomposition takes place, benzaldehyde is formed, and little product results.

6-Iodo-6-desoxy-2(3),5-benzylidene-monoacetyl-1,4-sorbitan.—A cold solution of 10 g. of 6-iodo-6-desoxy-2(3),5-benzylidene-1,4-sorbitan in 50 cc. of pyridine was treated with 9 g. of acetic anhydride. After several hours at room temperature, the reaction mixture was poured into ice water, crystallization occurring at once. The colorless product was twice recrystallized from 12 parts of ethanol in needles, melting at 126.5–127.5° (cor.), and rotating $[\alpha]^{25}D$ +40.4° (*c*, 3.16 in chloroform); yield, 10 g.

Anal. Calcd. for $C_{15}H_{17}O_5I$: C, 44.57; H, 4.24; I, 31.40. Found: C, 44.7, 44.4; H, 4.20, 4.31; I, 31.53.

6-Iodo-6-desoxy-2(3),5-benzylidene-monobenzoyl-1,4-sorbitan.—A cold solution of 10 g. of 6-iodo-6-desoxy-2(3),5-benzylidene-1,4-sorbitan in 50 cc. of pyridine was benzoylated with 11 g. of benzoyl chloride. After several hours at room temperature, the reaction mixture was poured into ice water, giving a solid product which was twice recrystallized from 25 parts of 95% ethanol in long colorless rods, melting at 139–141° (cor.), and rotating $[\alpha]^{25}D$ +73.8° (*c*, 4.84 in chloroform); yield, 12 g.

6-Iodo-6-desoxy-1,4-sorbitan.—A mixture of 50 g. of 6-iodo-6-desoxy-2,(3),5-benzylidene-1,4-sorbitan, 150 cc. of 95% ethanol, and 150 cc. of 0.2 *N* sulfuric acid, was immersed, under reflux condenser, in a boiling water-bath for just ten minutes. The homogeneous solution was rapidly cooled and extracted several times with 50-cc. portions of dichloromethane to remove benzaldehyde and unchanged starting material. The aqueous layer was neutralized with barium carbonate, filtered through Celite, and concentrated to dryness under reduced pressure, the bath temperature not exceeding 50°. The iodo-sorbitan crystallized out during the final stages of the distillation. Traces of water were removed by storing the flask containing the product in a desiccator overnight. The material was dissolved in 25 cc. of warm methanol, to which was then added 400 cc. of dichloromethane. On cooling and scratching, crystallization occurred. The product was filtered off and washed with dichloromethane, giving 28 g. of colorless product. An additional 4 g. was obtained by reworking the mother liquors; total yield, 32 g., or 85%. The material was recrystallized in excellent yield by dissolving in 25 cc. of methanol and adding 300 cc. of dichloromethane.

Anal. Calcd. for $C_6H_{11}O_4I$: C, 26.29; H, 4.05; I, 46.31. Found: C, 26.7, 26.1; H, 3.98, 4.07; I, 46.70.

6-Iodo-6-desoxy-1,4-sorbitan crystallizes in the form of 6-sided plates melting at 108–109° (cor.), and rotating $[\alpha]^{25}D$ −11.9° (*c*, 3.36 in water). It has a somewhat bitter taste, and is very soluble in water, alcohol and acetone, moderately soluble in hot ethyl acetate, and insoluble in ether, benzene and chloroform. It is rela-

tively unstable, showing signs of decomposition in several weeks when exposed to light, and in several months in the dark.

6-Tosyl-2,3,5-tribenzoyl-1,4-sorbitan.—To a solution of 10 g. (0.031 mole) of 6-tosyl-1,4-sorbitan in 100 cc. of pyridine, cooled in ice, was added 14.6 g. (0.10 mole) of benzoyl chloride. After standing twenty-four hours at room temperature, the reaction mixture was poured into water. The water layer was decanted from the sirupy product which precipitated. On stirring the sirup with 50 cc. of methanol, rapid crystallization occurred. After two recrystallizations from 10 parts of 95% ethanol, 18 g. (90% of theory) of colorless product was obtained in needles, melting at 106–107° (cor.),[10] and rotating $[\alpha]^{25}D$ +47.2° (*c*, 5.55 in chloroform), readily soluble in acetone, chloroform and benzene and insoluble in petroleum ether and water.

Anal. Calcd. for $C_{34}H_{30}O_{10}S$: C, 64.76; H, 4.80; S, 5.08. Found: C, 65.2, 64.5; H, 4.72, 4.76; S, 5.30.

6-Iodo-6-desoxy-2,3,5-tribenzoyl-1,4-sorbitan.—A solution of 19 g. (0.03 mole) of 6-tosyl-2,3,5-tribenzoyl-1,4-sorbitan and 9 g. (0.06 mole) of sodium iodide in 100 cc. of acetone was heated for one hour at 100° in a pressure flask. The precipitated sodium *p*-toluenesulfonate was filtered off, and the solvent removed from the filtrate. The residue solidified on addition of water, and was twice recrystallized from 600 cc. of 95% ethanol; yield, 15 g., 85%. The substance crystallized in plates melting at 151–153° (cor.) and rotating $[\alpha]^{25}D$ +5.1° (*c*, 2.92 in chloroform), insoluble in petroleum ether, ethyl ether and water and soluble in acetone, chloroform and benzene.

Anal. Calcd. for $C_{27}H_{23}O_7I$: C, 55.30; H, 3.95; I, 21.65. Found: C, 55.9, 55.2; H, 3.87, 3.87; I, 21.34.

Summary

1. A number of water soluble iodo-sugar derivatives have been prepared in order to study their utility as X-ray contrast agents in intravenous urography. These include 6-iodo-6-desoxy-D-galactose, 6-iodo-6-desoxy-α- and β-methyl-D-glucopyranosides, and 6-iodo-6-desoxy-1,4-sorbitan.

2. Several other new derivatives of 1,4-sorbitan have been synthesized.

3. β-Methyl-D-glucopyranoside has been prepared in 21% yield by treatment of glucose with methanolic hydrogen chloride, followed by isolation of the glucoside through its complex with potassium acetate.

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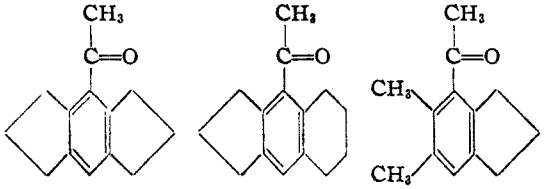
[CONTRIBUTION FROM THE SCHOOL OF CHEMISTRY OF THE UNIVERSITY OF MINNESOTA]

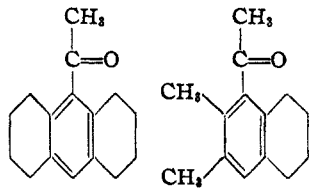
The Steric Effect of Methylene Groups. III

BY RICHARD T. ARNOLD AND PAUL N. CRAIG[1]

In an attempt to determine the relative steric influences of methylene groups in five- and six-membered rings, the following acetophenone derivatives have been prepared and examined.



(I) (II) (III)

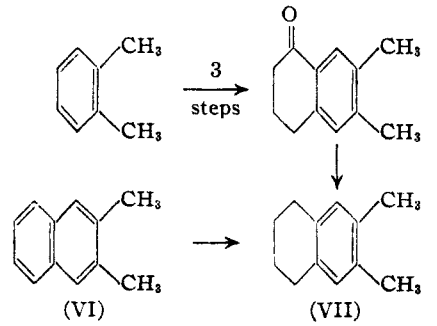


(IV) (V)

As reported earlier,[2] when treated with hypochlorite, acetohydrindacene (I) gives chloroform and 4-hydrindacenecarboxylic acid, whereas 9-acetoöctahydroanthracene (IV) gives a relatively stable trichloro ketone. The amount of methane evolved from methylmagnesium iodide (Zerewitinoff determination) decreases in the order IV > II > I. As a result of these observations and the values of carbonyl Raman frequencies, it was concluded that the steric hindrance around the carbonyl group decreases in the order IV > II > I.[2] Additional confirmatory evidence has now been obtained from observations on compounds III and V.

Of the above five ketones, only II is liquid; the others were readily purified by careful recrystallization. Tetrahydrobenz(f)indane, from which II is derived has now been prepared in a higher state of purity (m. p. 4°) and a sample of II obtained from this purer hydrocarbon has been reexamined.

6,7-Dimethyltetralin (VII) is obtained directly by catalytic reduction of 2,3-dimethylnaphthalene (m. p. 104°) in the presence of Raney nickel. The hydrocarbon so formed is essentially identical with that prepared from pure *o*-xylene.[3]



(VI) (VII)

It would appear that close approach to the cata-

(1) Du Pont fellow, 1947. Present address: Smith, Kline and French Company, Philadelphia, Pa.

(2) Arnold and Rondestvedt, THIS JOURNAL, **68**, 2176 (1946).

(3) Barnett and Sanders, *J. Chem. Soc.*, 434 (1933).