EXPERIMENTAL[11]

4-Benzoyl-2,3-diphenylbutyric acids. I. To a stirred suspension of 0.20 mole of sodium amide in 800 ml. of commercial anhydrous liquid ammonia[12] was added 13.6 g. (0.10 mole) of solid phenylacetic acid. The resulting green solution was stirred for 20 min., and 20.8 g. (0.10 mole) of solid benzalacetophenone was added. The color faded and a dark brown precipitate formed. After stirring for 1 hr., the mixture was neutralized by the addition of solid ammonium chloride (12 g.). The liquid ammonia was evaporated as an equal volume of ether was added. The resulting ethereal suspension was stirred with 300 ml. of 3*N* hydrochloric acid, and the ether was evaporated. Filtration of the remaining aqueous suspension afforded the isomeric keto acids Ia and Ib which were separated by a modification of the procedure of Avery and Jorgensen.[5]

Crystallization of the isomeric acids from glacial acetic acid (800 ml.) afforded 14.2 g. (41%) of *erythro* keto acid Ib, m.p. 258–261°. Recrystallization from glacial acetic acid raised the m.p. to 260–261° (lit.,[5] m.p. 260–261°). The methyl ester, prepared by refluxing the acid with methanol containing sulfuric acid, was crystallized from methanol, m.p. 177–178° (lit.,[5] m.p. 177–178°).

The original acetic acid filtrate was concentrated to 300 ml. and diluted with water at the boiling point until crystals appeared. The solid, which was deposited on cooling, was collected by filtration and was dissolved in 250 ml. of boiling benzene. After filtering to remove a small amount of insoluble material, the solution was cooled and filtered to give 12.4 g. (36%) of *threo* keto acid Ia, m.p. 182–184°. Recrystallization from benzene raised the m.p. to 186–187° (lit.,[5] m.p. 186–187°). The methyl ester, prepared by means of diazomethane, was crystallized from ethanol, m.p. 155–156° (lit.,[5] m.p. 155°).

Similar results were obtained when the ammonia was replaced by ether (without adding ammonium chloride) and ice was added to the ethereal suspension as previously reported.[2] The alkaline aqueous solution was acidified with 3*N* hydrochloric acid and the isomeric keto acids Ia and Ib were crystallized as described above.

threo-Enol-lactone IIIa. A solution of 3.14 g. (9.14 mmoles) of *threo*-keto acid Ia in 20 ml. of acetyl chloride was refluxed for 4 hrs. After cooling, the mixture was poured into 200 ml. of ligroin (b.p. 60–90°) and warmed to remov excess acetyl chloride. On cooling in ice there was obtained 2.45 g. (82%) of the *threo*-enol-lactone IIIa, m.p. 132–136°. Crystallization from glacial acetic acid–ligroin (b.p. 60–90°) afforded 1.85 g. (62%) of *threo*-enol-lactone IIIa, m.p. 138–139° (lit.,[5] m.p. 136°).

erythro-Enol-lactone IIIb. A mixture of 5.0 g. (0.0145 mole) of *erythro*-keto acid Ib and 75 ml. of thionyl chloride was refluxed for 5 hrs., and the excess thionyl chloride was then distilled. The residue was stirred with dilute sodium hydroxide solution and filtered. Crystallization from ethyl acetate afforded 1.2 g. (25%) of *erythro*-enol-lactone IIIb, m.p. 217–220° (lit.,[5] m.p. 220–222°).

When *erythro*-keto acid Ib was refluxed with acetyl chloride as described previously[5] only a 6% yield of the enol-lactone IIIb was obtained.

Epimerization of erythro keto acid Ib *through threo enol-lactone* IIIa. A solution of 2.0 g. (5.8 mmoles) of *erythro*-keto acid Ib in 25 ml. of acetic anhydride was refluxed for 24 hrs. After cooling, the solution was poured into 500 ml. of ligroin (b.p. 60–90°). The crystals which appeared on standing were filtered and discarded (m.p. 147–210°). Concentration of the filtrate to dryness afforded 1.4 g. (71%) of *threo* enol-lactone IIIa, m.p. 130–138°. The crude enol-lactone was dissolved in 20 ml. of glacial acetic acid, and the solution was heated to boiling. To the boiling solution there was added 14 ml. of 50% sulfuric acid, and the mixture was boiled for 5 min. The crude keto acid Ia, which crystallized on cooling, was filtered and recrystallized from benzene to give 1.0 g. (72% on lactone) of *threo* keto acid Ia, m.p. 186–188°. This m.p. was not depressed on admixture with an authentic sample obtained as described above.

Oxidation of threo enol-lactone IIIa. To a stirred solution of 1.6 g. (4.9 mmoles) of *threo*-enol-lactone IIIa in 100 ml. of glacial acetic acid at room temperature there was added during 25 min. a solution of chromium trioxide (1.0 g.) in 25 ml. of acetic acid and 6 ml. of water. The temperature was maintained below 35°. After stirring for 2 hr., 300 ml. of water was added, and the suspension was extracted with ether. The combined organic solutions were distilled under reduced pressure. The residue was dissolved in 50 ml. of ether and added to an ethereal solution of diazomethane. Acetic acid was added to decompose the excess diazomethane, and the solvent was distilled under reduced pressure to give *d,l*-dimethyl-2,3-diphenylsuccinate (0.25 g., 24%), m.p. 171–178°. Crystallization from *n*-propyl alcohol raised the m.p. to 177–178°. The *meso* dimethyl ester is reported[10] to melt at 221–222°. On admixture with the methyl ester of *erythro*-keto acid Ib, m.p. 177–178°, the m.p. was depressed to 152–173°.

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(11) Melting points were taken on a Fisher-Johns melting point apparatus and are uncorrected.

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Preparation of Methyl 2-Deoxy-2-sulfamino-α- and β-D-glucopyranoside Sodium Salts

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The presence of sulfamino group in heparin is generally accepted and appears to be in part responsible for the anticoagulant activity of the mucopolysaccharide.[1] Wolfrom, Gibbons, and Huggard[2] reported synthesis of methyl 2-deoxy-2-sulfamino-α-D-glucopyranoside, the β-isomer of which has not yet been reported. In this paper preparation of methyl 2-deoxy-2-sulfamino-α- and β-D-glucopyranoside sodium salts (monohydrates) (XI, XII) is described.

The glycosidation of 2-benzyloxycarbonylamino-2-deoxy-D-glucopyranose (I) was performed by refluxing it in methanol with Amberlite IR 120 (H^+). The product was a mixture of methyl 2-benzyloxycarbonylamino-2-deoxy-α- and β-D-glucopyranosides (II), but we could not separate the isomers at this step. After acetylation of II, with a mixture of pyridine and acetic anhydride, separation and recrystallization of methyl 3,4,6-tri-*O*-acetyl-2-benzyloxycarbonylamino-2-deoxy-α-and β-D-glucopyranosides (III, IV) were effected from ethanol. The β-isomer was more easily crystallizable than the α-isomer. The yield of the mix-

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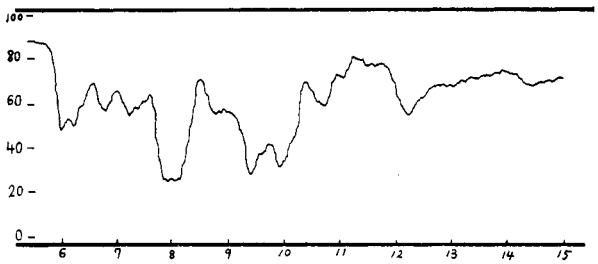

Fig. 1. Infrared spectrum of methyl 2-sulfamino-2-deoxy-α-D-glucopyranoside sodium salt (monohydrate) (XI), potassium bromide pellet

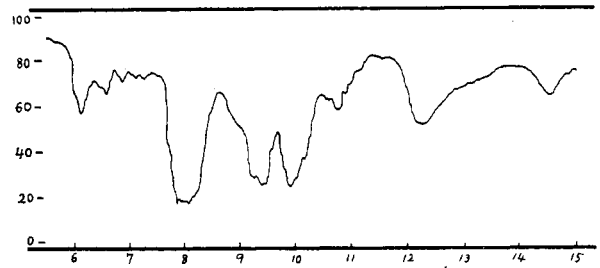

Fig. 2. Infrared spectrum of methyl 2-sulfamino-2-deoxy-β-D-glucopyranoside sodium salt (monohydrate) (XII), potassium bromide pellet

ture of III and IV was 80% and, after separation, the proportion of the yields of the α-isomer, the β-isomer and of the mixture of both the isomers was 45, 50, and 5, respectively. This acetate procedure is more convenient for the separation of α- and β-isomers than those reported previously.[3,4]

Benzyloxycarbonyl residue of the compound (III, IV) was removed by catalytic hydrogenation, and the resultant amino sugars were isolated as hydrochlorides (V, VI) which were treated with Amberlite IRA 400(OH^-) to give rise to methyl 3,4,6-tri-*O*-acetyl-2-amino-2-deoxy-β-D-glucopyranoside (VIII) and -α-D-glucopyranoside (VII), respectively.

Sulfation procedures are described in several reports.[2,5-15] In the present work sulfation was performed with sulfur trioxide–pyridine complex in pyridine solution.[2,5] The acetylated product was deacetylated with sodium methoxide to give methyl 2-deoxy-2-sulfamino-β-D-glucopyranoside sodium salt (monohydrate) (XII) [or -α-D-glucopyranoside sodium salt (monohydrate) (XI)], which was amorphous and very hygroscopic. This compound was negative for the ninhydrin test and the Elson-Morgan reaction, but was positive for both the tests after hydrolysis with hydrochloric acid.

The infrared absorption of methyl 2-deoxy-2-sulfamino-α- and β-D-glucopyranoside sodium salts (monohydrates) (XI, XII) showed strong absorption bands of sulfate at 1230–1265 $cm.^{-1}$, medium at 817 $cm.^{-1}$, and weak at 930–932 $cm.^{-1}$ It is noted that the α-isomer showed a peak at 910 $cm.^{-1}$, whereas the β-isomer peak was at 918 $cm.^{-1}$ (Fig. 1). The infrared absorption of heparin shows other bands which are attributed to C—O—S vibrations.[16-21] It is also mentioned that sulfated polysaccharides show absorption bands at 1240 $cm.^{-1}$ and 820–850-$cm.^{-1}$ regions.[16-21]

EXPERIMENTAL[22]

Methyl 2-benzyloxycarbonylamino-2-deoxy-α,β-D-glucopyranoside (II). Ten grams of 2-benzyloxycarbonylamino-2-deoxy-D-glucose (I) was dissolved in 500 ml. of methanol and the solution was refluxed for 3 to 3.5 hr. with 20 g. of Amberlite IR 120 (H^+) as the catalyst.[23-25] After removal of ion exchange resin, the pale-yellow methanolic solution was decolorized and was concentrated under reduced pressure to dryness. The white pasty product was dried in a vacuum desiccator to yield white powder. Recrystallization from ethanol afforded white crystals, melteing at 156–159°, $[\alpha]^{28}D$ +18°, (*c* 1, pyridine), yield, 10.4 g. (92%).

Anal. Calcd. for $C_{15}H_{21}O_7N$: C, 55.04; H, 6.14; N, 4.28. Found: C, 55.13; H, 5.91; N, 4.26.

The separation of α- and β-isomers was not successful at this step. The reported $[\alpha]D$ for the α-isomer is +80° [3]; +88° [4]; that for the β-isomer, −38° [3]; −35° [4].

Methy 3,4,6-tri-O-acetyl-2-benzyloxycarbonylamino-2-deoxy-α- and β-D-glucopyranosides (III, IV). Ten grams of II was acetylated with a mixture of 50 ml. of pyridine and 50 ml. of acetic anhydride at room temperature for 20 hr. The reaction mixture was poured onto ice-water and was stirred vigorously. The solid matter was collected by filtration and then was dissolved in a large amount of hot ethanol and was decolorized. After standing the solution in a refrigerator,

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white crystalline matter separated. This was collected by filtration and was recrystallized from ethanol. Yield, 3.3 g. (50%), m.p. 147–148°, $[\alpha]^{29}D$ +3.4° (*c* 1, pyridine).

Anal. Calcd. for $C_{21}H_{27}O_{10}N$: C, 55.62; H, 6.00; N, 3.09 Found: C, 55.12; H, 5.93; N, 3.33. $[\alpha]D$ showed that the above crystal was the β-isomer (IV).

The filtrate was concentrated under reduced pressure to a small volume and was placed in a refrigerator, whereupon crystals separated. Repeated recrystallization from ethanol yielded 3.0 g. of fine needles (45%), m.p. 102–105°, $[\alpha]^{29}D$ +104° (*c* 1, pyridine).

Anal. Found: C, 55.39; H, 5.95; N, 3.30. The constants showed that the crystal was the α-isomer[2] (III).

Methyl 3,4,6-tri-O-acetyl-2-amino-2-deoxy-β-D-glucopyranoside hydrochloride (VI). An amount of 5 g. of IV was dissolved in 100 ml. of methanol, and to this was added 1 g. of palladium-on-barium sulfate catalyst. The solution was stirred for few minutes, with dry hydrogen gas bubbling through, and to this was added half of 0.011 mole of dry methanolic hydrogen chloride. Another half portion of methanolic hydrogen chloride was added after 1.5 hr., and the reaction was completed within 3 hr. After removal of catalyst, the solution was concentrated under reduced pressure to a small volume, and to this was added a large amount of ether. A white crystalline substance separated. Recrystallization was effected from ethanol-ether. Yield, 3.0–3.2 g. (78–83%). Methyl 3,4,6-tri-O-acetyl-2-amino-2-deoxy-β-D-glucopyranoside hydrochloride (VI) melted at 216–227° (dec.). $[\alpha]^{25}D$ +10° (*c* 1, water).

Anal. Calcd. for $C_{13}H_{22}O_8NCl$: C, 43.89; H, 6.23; N, 3.94 Found: C, 43.99; H, 6.35; N, 4.11.

Methyl 3,4,6 - tri - *O* - acetyl - 2 - amino - 2 - deoxy - α-D-glucopyranoside hydrochloride (V) melted at 225–233° (dec.). $[\alpha]^{23}D$ +157.8° (*c* 1, water).

Anal. Found: C, 43.79, H 6.28, N 3.85. Reported constants,[2] m.p. 230–238°, $[\alpha]^{26}D$ +154° (*c* 1.8, water).

Methyl 3,4,6-tri-O-acetyl-2-amino-2-deoxy-β-D-glucopyranoside (VIII). Five grams of VI was dissolved in a small amount of 50% aqueous methanol and the solution was passed through a column (20 × 2 cm. diam.) of Amberlite IRA 400 (OH^-) and the effluent was concentrated under reduced pressure. The product was a sirup, dried over phosphorus pentoxide, and was used in the next reaction. Methyl 3,4,6-tri-*O*-acetyl-2-amino-2-deoxy-α-D-glucopyranoside (VII) was also a sirup.

Methyl 3,4,6-tri-O-acetyl-2-deoxy-2-sulfamino-β-D-glucopyranoside sodium salt (X). VIII was dissolved in 60 ml. of anhydrous pyridine and to this was added the sulfation reagent[2,5] which was freshly prepared by the slow addition of 3 ml. of sulfur trioxide to 50 ml. of anhydrous pyridine previously cooled to −15°. The reaction mixture was shaken for 20 hr. at room temperature with the exclusion of moisture. A pale-yellow sirupy substance was obtained. This was poured into 700 ml. of water containing 4 g. of sodium bicarbonate, and the resultant solution was concentrated under reduced pressure. It was extracted three times with ethyl acetate-methanol, and the extract was concentrated under reduced pressure to a sirup. Methyl 3,4,6-tri-*O*-acetyl-2-deoxy-2-sulfamino-α-D-glucopyranoside (IX) could not be obtained in crystalline form.

Methyl 2-deoxy-2-sulfamino-β-D-glucopyranoside sodium salt (XII). The above obtained sirup (X) was dissolved in methanol and was decolorized, and to this was added 0.05 mole of sodium methoxide to effect deacetylation. The reaction mixture was kept at room temperature for 20 hr., and the solvent was removed under reduced pressure to give a sirup. To this was added a large amount of ethanol, and the solution was stored overnight in a refrigerator. The amorphous precipitate was collected by centrifugation. Repeated recrystallizations from methanol-ethanol yielded 2 g. (4%, based on VI) of white powder which was very hygroscopic. The product was negative for the ninhydrin test and the Elson-Morgan reaction but was positive for both the tests after hydrolysis with 2.5 *N* hydrochloric acid at 100°. M.p. 193–197° (dec.), $[\alpha]^{25}D$ +5.0° (*c* 1, water).

Anal. Calcd. for $C_7H_{14}O_8NSNa \cdot H_2O$: C, 26.8; H, 5.1; N, 4.5; S, 10.2; Na, 7.3. Found: C, 27.3; H, 5.3; N, 4.3; S, 10.3; Na, 7.4. This compound seems to be a monohydrate. Methyl 2-deoxy-2-sulfamino-α-D-glucopyranoside sodium salt (monohydrate) (XI) melted at 175–178° (dec.), $[\alpha]^{26}D$ +105.9° (*c* 1, water).

Anal. Found: C, 27.3; H, 5.3; N, 4.4; S, 10.1; Na, 7.7. The reported constants[2] for the compound (XI) are m.p. 159–161°, $[\alpha]^{27}D$ +103.1° (*c* 2.1, water).

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The Synthesis of Dicyclopropyl Ethers[1]

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The direct synthesis of the previously unknown class of compounds, dicyclopropyl ethers, was made possible by the recent availability of a series of divinyl ethers.[3] The addition of carbenes to monovinyl ethers was previously noted by Doering[4] to proceed more rapidly than similarly substituted olefins. Consequently, the divinyl ethers were expected to allow isolation of reasonable yields of dicyclopropyl ethers upon reaction with carbenes, even though the divinyl ethers could not be used in excess as are mono-unsaturated reactants.

The generation of dichlorocarbene from chloroform in the presence of the unsubstituted divinyl ether (I) by the action of potassium *tert*-butoxide resulted in polymerization of the divinyl ether. Similarly, bromoform and benzal dichloride with potassium *tert*-butoxide in the reaction gave the same results. The use of *n*-butyllithium and methylene dichloride was also unsuccessful as the butyllithium also caused polymerization of the divinyl ether. However, the slow addition of ethyl trichoroacetate to sodium methoxide in a petroleum ether solution of I yielded the desired bis(2,2-dichlorocyclopropyl) ether (III). Compound III was a very high boiling viscuous compound which was purified by evaporative distillation at low pressure.

As I was so sensitive toward polymerization, a more stable divinyl ether was sought. The synthetically available diisobutenyl ether (II) exhibited a high degree of stability toward base and was consequently used. According to previous observations, the higher substitution of this ether

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(2) Abstracted from the doctoral thesis of Karl F. Schimmel, Duquesne University, 1961.

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