the ratios were 3.84:3.00:1.00:1.22. The reaction mixture was cooled, filtered to remove metallic iron, and treated with 2.9 g (0.0182 mol) of ferric chloride in 20 ml of 95% ethanol. Gas evolution (CO) was noticed. This mixture was stirred for 2 hr, poured into salt water, and extracted with pentane. Distillation of the pentane extract, with tridecane added as a chaser solvent, yielded a fraction of bp 71–85° (18–20 mm) which contained octane, ester isomers, and tridecane. This mixture weighed 5.1 g, of which 4.1 g (92% recovery after correction for aliquot samples) was ester isomers as determined by quantitative gc. The ratio of gc peaks remained constant before and after ferric chloride treatment and distillation. An nmr spectrum showed peaks at 3.2 (β-vinyl H, 2 isomer), 4.35 (α-vinyl H, 2 isomer), 4.7 (vinyl H, internal isomers), 6.45 ($-CO_2CH_3$), 7.15 ($C{=}C-CH_2-CO_2-$), and other normal peaks of olefin ester internal isomers. Integration of the aforementioned peaks showed 20.2% of the 2 isomer and 9.6% of the 3 isomer. The mixture was analyzed by oxidative cleavage (Table I) to obtain the per cent of other internal isomers and to substantiate the nmr result.

An alternative in the work-up involved leaving out the ferric chloride treatment and destroying most of the $Fe(CO)_5$ catalyst by heating. In these cases the product was analyzed directly after filtration to remove metallic iron. Analyses of isomerized mixtures by gas chromatography were checked by preparing known molar concentration solutions of standards. For example, a prepared mixture of methyl cyclohexene carboxylate isomers containing 43.8% of the 1, 22.7% of the 2, and 34.5% of the 3 isomer was shown by gas chromatography to have 46.2% of 1-, 21.3% of 2-, and 32.5% of 3-cyclohexene carboxylates.

Irradiation Induced Iron Carbonyl Catalyzed Isomerization of Alkenyl Ethers.—An example of these reactions is the isomerization of methyl 4-pentenyl ether. To a solution of 1.0 g (0.01 mol) of methyl 4-pentenyl ether in 135 ml of deoxygenated pentane, was added 0.1 g (0.07 ml, 5×10^{-4} mol, ~5 mol %) of iron pentacarbonyl. The solution was irradiated with a 200-W high pressure mercury lamp (Type S, 654A-36 Hanovia lamp, Engelhard Hanovia, Inc., Newark, N. J.) with argon bubbling through the solution for a 3-hr period. At 1-hr intervals, the irradiation was stopped and 3-ml samples were withdrawn and analyzed by infrared and gas chromatography after removal of most of the pentane by distillation. Infrared bands at 6.0, 8.0, and 10.7 μ indicated that within 1 hr most of the starting material had been converted into methyl *cis* and *trans* 1-pentenyl ethers. Analysis by gas chromatography showed two peaks of relative area 1:2.66. After 3 hr, an additional 5% of iron pentacarbonyl was added and the solution irradiated for 3 more hr. No change in infrared or gas chromatography analyses was detected after this period. The mixture was filtered to remove insoluble metal carbonyls and pentane solvent was removed by distillation. The total of 900 mg (~97%) of unpurified product was recovered. Gas chromatography analysis of this product indicated 97% of this mixture was methyl pentenyl ether isomers.

During some of the reactions a dark film was deposited on the immersion well of the reactor, decreasing the transmittance of ultraviolet light. The isomerization reactions were stopped when this occurred, the well was cleaned with sulfuric acid, and the reactions were continued.

Registry No.—Iron pentacarbonyl, 13463-40-6.

Acknowledgment.—We wish to thank Drs. T. J. Logan and C. D. Broaddus for reading the manuscript and for stimulating discussions of this work. We are particularly indebted to Dr. D. E. O'Connor and Professor W. von E. Doering for helpful suggestions concerning this study.

The Total Synthesis of (±)-1-Deaza-1-thiareserpine[1a]

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The potential antihypertensive, (±)-1-deaza-1-thiareserpine (**10**), is described by way of its seven-step synthesis from the methyl ester of (±)-2α-methoxy-3β-hydroxy-5-ene-7-keto-1,2,3,4,7,8-*cis*-9α,10α-octahydro-1β-naphthoic acid, 4,3,4,5-trimethoxybenzoyl chloride (**5**), and 6-methoxy,3-(2-aminoethyl)benzo[*b*]thiophene (**3**).

Reserpine, isolated from *Rauwolfia serpentina* Benth, has been used clinically for a number of years as an antihypertensive. Its adverse side effects, together with our continuing interest in the field of sulfur-containing pharmaceuticals, has prompted our synthesis of a modified reserpine in which the indole nitrogen is replaced by the thianapthyl sulfur, *viz.* 1-deaza-1-thiareserpine (**10**).

The brilliant total synthesis of the natural reserpine molecule by Woodward and his coworkers[2] formed the basis of our synthetic development. Advantage was taken of other more recent work[3] to reduce the number of individual steps in our total synthesis of thiareserpine.

Since the benzo[*b*]thiophene molecule follows closely much of the electrophilic substitution chemistry of indole,[4] it was anticipated that the reactions to effect condensation of the molecules shown in Scheme I would proceed without difficulty and yield intermediates of unambiguous structures.

Thus, our initial synthetic attempts were directed toward the preparation of the previously unknown 6-methoxy-3-(2-aminoethyl)benzo[*b*]thiophene (**3**). Earlier work in our laboratories indicated that a feasible synthesis of this amine would be difficult by direct replacement of intermediate substituents on the thianapthene nucleus.[5] Therefore, the desired precusor, **3**, was formed by building the thiophene ring onto the benzene ring (Scheme II). Ethyl 4-chloro-3-ketobutyrate was treated with *m*-methoxybenzenethiol in pyridine to form the sulfide, **1**, which on ring closure with polyphosphoric acid and subsequent ammonolysis gave a mixture of 6-methoxy- and 4-methoxythianapthenes in a 20:1 ratio. Separation of the isomers was accomplished by fractional crystallization. The structure of the desired amide, **2**, 6-mehtoxy-3-thianaphthyl acid, was established by hydrolysis to its corresponding acid, followed by Raney

(1) (a) Presented in part at the 154th National Meeting of the American Chemical Society, Chicago, Ill., Sept 1967. (b) To whom all correspondence should be addressed at the Institute of Biology and Medicine, Department of Chemistry. (c) Abstracted in part from the Master's Dissertation of G. P. Nilles and the Doctoral Dissertation of R. L. Titus.

(2) R. B. Woodward, F. E. Bader, H. Bickel, A. J. Frey, and R. W. Kierstead, *Tetrahedron*, **2**, 1 (1958).

(3) For examples see E. Schlittler in "The Alkaloids," Vol. 8, R. H. F. Manske, Ed., Academic Press Inc., New York, N. Y., 1965, Chapter 13.

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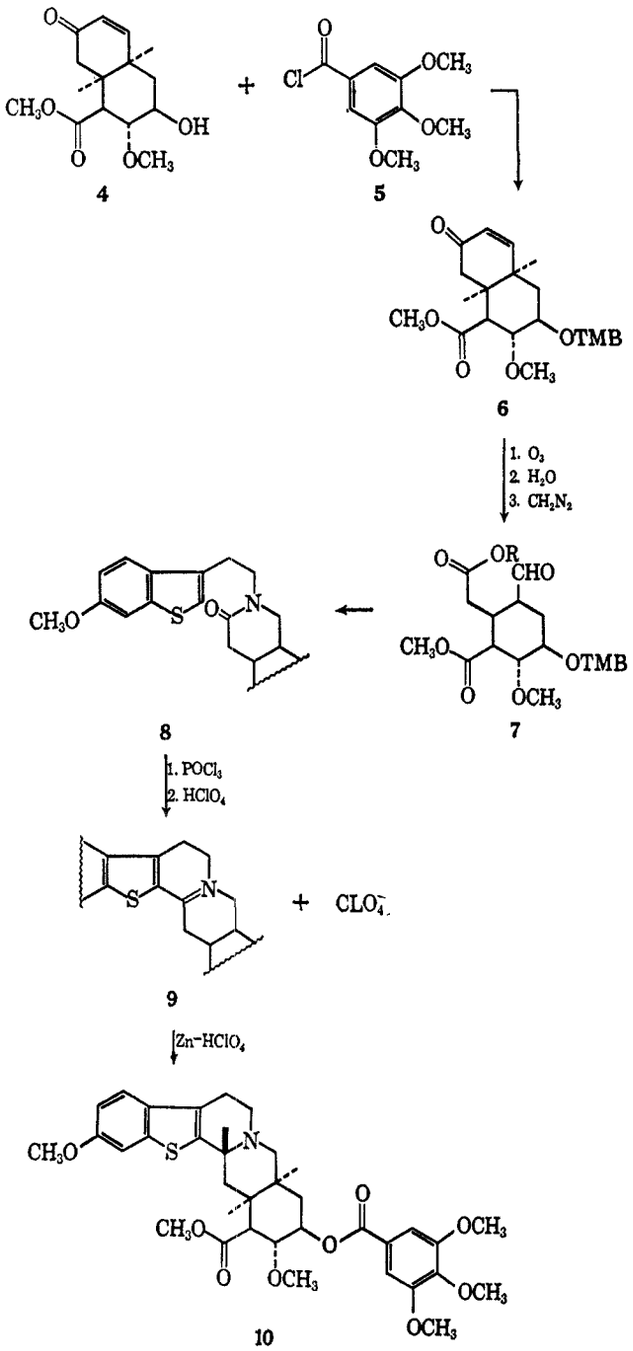
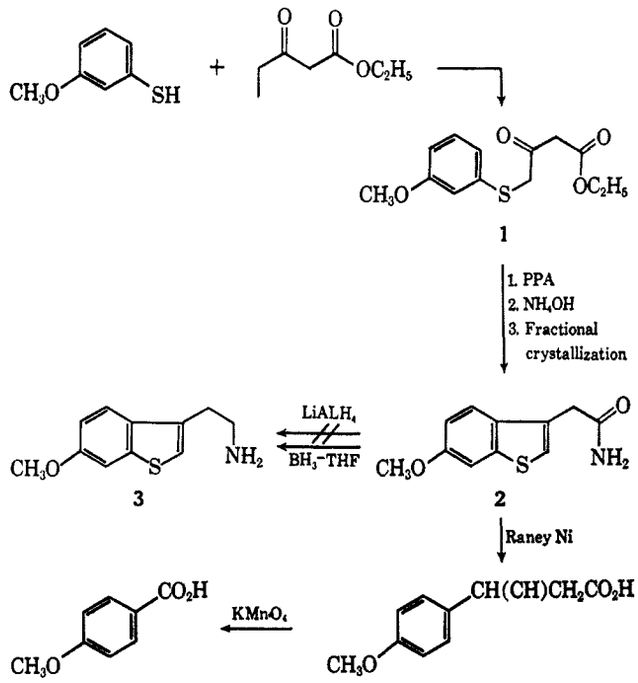
(5) R. L. Titus, Doctoral Dissertation, Michigan State University, East Lansing, Mich., 1964.

SCHEME I



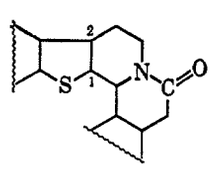
SCHEME II



nickel desulfurization to yield β-(methoxyphenyl)butyric acid, whose nmr spectrum showed a doublet at τ 8.7 (J = 7Hz) for the branched methyl group. Oxidation of the latter acid formed the known p-anisic acid. The 6-methoxy- and 4-methoxy-3-thianapthylacetic acids formed by saponification of the corresponding amides were submitted for evaluation as plant growth stimulants. The 4-methoxy compound was found to be only slightly less active than indole-3-acetic acid in *Avena* species. The 6-methoxy isomer was inhibitory at concentrations up to 10^{-5} M at which concentration it was slightly active as a growth promoter.[6]

Lithium aluminum hydride reduction of **2** failed to yield the amine[5] **3**; however, on treatment with borane–tetrahydrofuranate[7] a practicable yield of **3** was obtained.

Compound **4** prepared by Woodward's procedure[2] was treated with **5** to yield the diester acid **6** as shown in Scheme I. A previous publication[8] had shown the feasibility of forming **7** (R = H) directly from **6** by ozonolysis. Application of this process led to the aldehyde **7** (R = H). It was characterized as the previously unknown 2,4-dinitrophenylhydrazone. Treatment of **7** (R = H) with diazomethane led to the triester **7** (R = CH_3), which was condensed with **3** to give an imine. The imine on reduction with sodium borohydride readily gave the lactam **8** *via* internal ammonolysis. The formation of a 1,2,3,4-tetrahydrobenzothieno[2,3-*c*]pyridine system *via* a Pictet–Spengler-type condensation (**11**) was ruled out on the basis of elemental analysis (the desired lactam **8** has C–H



13

(10.091:1); structure **11** has C–H (10.626:1, found 10.133:1), stability of the yellow imine precursor in solution and a previous report[9] that condensations of this type lead to the desired system. A Bishler–Napieralski-type ring closure of the amide followed by treatment with perchloric acid gave the highly fluorescent (±)-1-deaza-1-thia-3,4-dehydroreserpine perchlorate (**9**). When subjected to reduction by zinc in perchloric acid, the desired (±)-1-deaza-1-thiareserpine (**10**) resulted. It was shown to be homogeneous by thin layer chromatography on alumina. That the C-3

(6) Complete details concerning these compounds as well as other 3,6- and 3,4-dissubstituted thianaphthenes are described in a publication: R. D. Schuetz and R. L. Titus J. *Heterocycl. Chem.*, **4**, 465 (1967).

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hydrogen possessed the β configuration was shown by an extension of the work of Wenkert[10] and Protiva.[9] Wenkert found that epiallo yohimbanes, such as reserpine, do not have an absorption at 2740 cm^{-1}, while the allo systems (*i.e.*, the C-3 epimer) do. Protiva[9] in his synthesis of (±)-1-deaza-1-thiadeserpidine showed this system also lacked this absorption, while the C-3 epimer (α hydrogen) absorbed at 2760 cm^{-1}. The infrared spectrum of (±)-1-deaza-1-thiareserpine does not have this absorption. Further support of the stereochemistry comes from a publication by Vellux,[11] that zinc–perchloric acid reduction of the immonium salt in his synthesis of reserpine led exclusively to the C-3 hydrogen being β oriented.

By obtaining this "thiareserpine" in an over-all yield at 0.2% it is hoped that a new useful pharmaceutical is at hand. Work toward establishing its pharmacologic response will be undertaken and reported subsequently.

Experimental Section

Melting points were taken with an electrothermal melting point apparatus calibrated with furnished standards. Ultraviolet spectra were determined on a Beckman DK-2A instrument in 95% ethanol. Infrared spectra were run on a Perkin-Elmer 237B grating spectrophotometer.

Ethyl 4-(*m*-Methoxyphenylmercapto)-3-oxobutyrate (1).—A mixture of 35.8 g (0.256 mol) of *m*-methoxybenzenethiol[12] in 180 ml of pyridine cooled to 0° was treated in a dropwise manner with 41.9 g (0.256 mol) of ethyl 4-chloro-3-ketobutyrate maintaining the reaction temperature below 25–30°. After heating to 70–80° for 10 min and then recooling, the reaction solution was adjusted to pH 5 with 6 *N* hydrochloric acid. The resulting oil was separated and combined with the ether extracts (two 50-ml portions) of the aqueous layer. Removal of the solvent gave 62.4 g (0.233 mol, 91.0%) of the crude product.

Ethyl 6-(4)-Methoxythianaphthyl-3-acetate.—A mixture of 30.6 g (0.114 mol) of crude **1**, 50 ml of 85% orthophosphoric acid, and 100 g of phosphorus pentoxide in 200 ml of chlorobenzene was refluxed for 3 hr. The chlorobenzene was decanted and replaced with 200 ml of benzene, and the mixture underwent reflux for 3 hr. The combined aromatic solvents were washed successively with 10% sodium bicarbonate (50 ml) and water (two 50-ml portions). Removal of the solvents gave 25.6 g (0.120 mol, 90.5%) of the mixed esters which were used directly in the next step of the synthesis.

6-(4)-Methoxythianapthyl-3-acetamide (2).—The mixed esters, 17.0 g (0.0692 mol), were stirred continuously for 7 days in 400 ml of concentrated ammonium hydroxide at room temperature. The gummy amide was crystallized from hot ethanol and recrystallized to yield 4.82 g (0.0218 mol, 31.7%), mp 192–193°, of the pure 6-methoxy isomer as the less soluble product. Chromatography of the mother liquor residue, from the above fractional crystallization, on a 3 × 45 cm alumina column (Matheson activated alumina, 80–200 mesh, dried at 200° for 18 hr) after elution with chloroform and collection in 50-ml fractions gave the 4-methoxy isomer in fractions 10–13. It was recrystallized from a small amount of ethanol to give 0.24 g of product, mp 199–200°. Desulfurization of the 6-methoxy product with Raney nickel in the usual manner, followed by oxidation of the product with potassium permangamate, gave only *p*-anisic acid (by melting point determination and infrared analysis) as the product.

Anal. Calcd for $C_{11}H_{11}O_2NS$: C, 59.72; H, 5.01; N, 6.36; S, 14.47. Found for 6-methoxyamide: C, 60.21; H, 5.14; N, 6.22; S, 14.37. Found for 4-methoxyamide: C, 59.83; H, 5.08; N, 6.47; S, 14.42.

6-Methoxy-3-(2-aminoethyl)benzo[*b*]thiophene (3).—To a cold (0°) stirred 1 *M* solution of boran–tetrahydrofuranate (Metal Hydrides, Inc., Beverly, Mass., 40 ml, 0.040 mol) was added 1.10 g (5.00 mmol) of **2** in a single portion under nitrogen pressure. Following 8 hr of refluxing, the reaction mixture was set aside at room temperature for 16 hr and then 20 ml of 6 *N* hydrochloric acid was carefully added to the mixture. Removal of the tetrahydrofuran under reduced pressure, basification to a pH of 10 with 5 *M* sodium hydroxide, extraction with three 50-ml portions of ether, and removal of the ether gave the desired amine. The amine was distilled to yield 0.636 g (3.08 mmol, 61.4%), bp 130–140° (0.3 torr), n^{25}°D 1.5964. The amine was protected from atmospheric carbon dioxide by storage under nitrogen. A picrate was prepared in the usual manner and recrystallized three times from ethanol, mp 177–178°.

Anal. Calcd for $C_{17}H_{16}N_4SO_8$: C, 46.78; H, 3.69; N, 12.84; S, 7.35. Found: C, 46.60; H, 4.26; N, 12.77; S, 7.31.

(±)-2α-Methoxy-3β-(3′,4′,5′-trimethoxybenzyloxy)-5-ene-7-keto-1,2,3,4,7,8-*cis*-9α-10α-octahydro-1β-naphthoic Acid Methyl Ester (6).—From 0.500 g (1.98 mmol) of **4**[2,13] 0.701 g (1.50 mmol, 79.0%) of **6** was prepared, employing the method of Veichet, Pelz, and Bláha.[8] The product had bands at λ_{max} 217 mμ (ε 38,300) and 268 mμ (ε 10,900).

(±)-1-Deaza-1-thia-2,3-seco-3-oxoreserpine (8).—A 224-mg (0.500 mmol) quantity of **6** was ozonized in 10 ml of anhydrous methylene chloride using 1% O_3 in O_2 and employing 5% aqueous potassium iodide as an external indicator. The reaction mixture, following ozonolysis, was purged with dry nitrogen for 10 min and then heated at reflux for 45 min, under nitrogen, with 2 ml of water containing 0.01 g of hydroquinone. After separating the layers and extracting the aqueous layer with two 5-ml portions of methylene dichloride, the solvents were combined and dried with sodium sulfate. A 2,4-dinitrophenylhydrazone prepared at this point was recrystallized three times from ethanol, mp 128–131°.

Anal. Calcd for $C_{28}H_{32}O_{14}N_4$: C, 51.88; H, 4.97. Found: C, 51.60; H, 5.10.

The methylene chloride solution of **7** (R = H) was cooled to 0° and treated with a slight excess of ethereal diazomethane. After 10 min, half of the solvent was removed at reduced pressure under nitrogen. After recooling to 0°, a solution of 104 mg (0.503 mmol) of **3** in 1.4 ml of benzene was added in a single portion. After 10 min the yellow orange solution was treated at 0° with 19.0 mg (0.500 mmol) of sodium borohydride in 2 ml of anhydrous methanol during a period of 5 min. Acetic acid was added (two drops) and all solvents were removed under nitrogen at water pump pressure and finally with an oil pump at 0.01 torr. The thoroughly dried lactam **8** was purified by repetitive precipitation from ethyl acetate by adding ether to yield 240 mg (0.374 mmol, 74.8%), mp 145–148° dec (sealed capillary). The ultraviolet spectrum showed λ_{max} at 214 mμ (ε 51,100), 244 shoulder (15,600), and 267 (15,600).

Anal. Calcd for $C_{33}H_{39}O_{10}NS$: C, 61.76; H, 6.12; S, 5.00. Found: C, 61.51; H, 6.07; S, 4.67.

(±)-1-Deaza-1-thia-3,4-dehydroreserpine Perchlorate (9).—A solution of 100 mg (0.156 mmol) of **8** in 2 ml of freshly distilled phosphorous oxychloride was heated at 65° under nitrogen for 45 min. After removal of the solvent at water pump pressure, the reaction mixture was taken to dryness at 0.01 torr. The residue, dissolved in 4 ml of acetone, was treated with 3.5 ml of 0.1 *N* perchloric acid. The acetone was removed under a reduced nitrogen atmosphere and the aqueous suspension was extracted three times with 5-ml portions of chloroform. After drying the combined extracts with sodium sulfate, the solvent was removed to dryness. The residue was triturated with ether and collected to yield 101 mg (0.140 mmol, 89.8%) of **9**. For analysis it was recrystallized from ethanol–acetone, 5:1, mp 203–205° dec (sealed capillary). The infrared spectrum (KI pellet) showed λ_{max} at 1720 (C=O) and 1600 mμ (C=$\overset{+}{N}$<); the ultraviolet spectrum showed λ_{max} at 213 mμ (ε 44,800), 269 (19,300), 382 (9780).

Anal. Calcd for $C_{33}H_{38}O_{13}NSCl$: C, 54.80; H, 5.29; N, 1.94; S, 4.43. Found: C, 54.28; H, 5.53; N, 2.07; S, 4.64.

(±)-1-Deaza-1-thiareserpine (10).—A 111-mg (0.153 mmol) quantity of **9** was dissolved in a mixture of 5 ml of acetone and 1.5 ml of 0.7 *N* perchloric acid along with sufficient tetrahydrofuran to form a clear solution. The mixture was stirred and heated at 70° under nitrogen, and 0.15 g of zinc dust was added. After 10 min of reaction a second 0.15-g portion of zinc dust was added and this addition was repeated after another 10 min of reaction.

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(13) This material was identical by melting point determination and infrared spectrum with that reported.

Following another 10 min of reaction the characteristic fluorescence of the immonium salt (9) had almost disappeared and the reaction mixture was cooled to room temperature. After filtration and basifying to a pH of 9 with concentrated ammonium hydroxide, 10 ml of chloroform was added. The layers were separated and the aqueous layer was extracted twice with 5-ml portions chloroform. The chloroform extracts were combined, dried with sodium sulfate, filtered, and evaporated under a reduced nitrogen atmosphere. The residue (71 mg) was triturated with 10 ml of boiling ethanol, filtered hot, and concentrated to 3 ml. With constant stirring, 15 ml of ether was added and the resulting precipitate (54 mg, 0.086 mmol, 56%) of (±)-1-deaza-1-thiareserpine was collected. A small quantity (~1 mg) was subjected to thin layer chromatography on Woelm activity II alumina elution with a mixture of chloroform–methanol–benzene (10:3:1)) and showed a single dark spot (R_f 0.65) under ultraviolet light. Recrystallization from ethanol–ether (9:1) gave an analytical sample (21 mg), mp 188–191° (sealed capillary), of fine, pure white crystals. The infrared spectrum of thiareserpine ($CHCl_3$) showed absorption at 3032, 2930, 2860, 1735, 1590, 1505, 1465, 1420, 1340, 935, 800, 720, 680 cm^{-1}. The ultraviolet spectrum had λ_{max} at 213 mμ (ε 58,700), 231 shoulder (27,100), 244 shoulder (20,200), 267 (22,200).

Anal. Calcd for $C_{33}H_{39}O_9NS$: C, 63.34; H, 6.28; N, 2.24. Found: C, 63.08; H, 6.75; N, 2.53.

Registry No.—4-Methoxythianaphthyl-3-acetamide, 14679-05-1; 6-methoxythianaphthyl-3-acetamide, 14679-06-2; **3**, 14679-07-3; picrate of **3**, 14679-49-3; 2,4-dinitrophenylhydrozone of **7** (R = H), 14679-08-4; **8**, 14745-99-4; **9**, 14679-09-5; **10**, 14679-10-8.

The Synthesis of Three Fully Acetylated Aldobiouronic Acid Methyl Esters, Including 6-*O*-(Methyl 2,3,4-tri-*O*-acetyl-α-D-glucopyranosyluronate)-tetra-*O*-acetyl-β-D-glucopyranose

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6-*O*-α-D-Glucopyranuronosyl-D-glucose (isomaltouronic acid) is a possible moiety in the capsular polysaccharide of *Diplococcus pneumoniae* Type II. The synthesis of its fully acetylated methyl ester starting from β-isomaltose octaacetate is described. Improvements in the syntheses of the fully acetylated methyl esters of 6-*O*-β-D-glucopyranuronosyl-D-glucose (gentiobiouronic acid) and 4-*O*-α-D-glucopyranuronosyl-D-glucose (maltouronic acid) are also reported.

The structure of the capsular polysaccharide of *Diplococcus pneumoniae* Type II has been under investigation for some time.[2-5] It is known that this antigenic capsular polysaccharide, S-II, contains terminal as well as intercatenary glucuronic acid residues. Recent additional findings[6] concerning the structure of S-II have clarified much about the type of linkages involved in this polysaccharide as well as some of the anomeric configurations. Still, the anomeric configuration of the intercatenary, presumably 1–6 linked, glucuronosylglucose is still open to question. Comparison of the inhibition of the antigen–antibody precipitation in the S-II–anti S-II system by isomaltouronic acid and gentiobiouronic acid could yield information about the anomeric configuration of this linkage. Similarly, the inhibition of the same system by maltouronic and cellobiouronic acids could shed light on the immunological importance of the anomeric configuration of the terminal glucuronosyl linkage.

The terminal uronic acid in S-II behaves unexpectedly, in that, although the molecule has terminal cellobiouronic acid units,[6] rabbit serum obtained against a synthetic antigen containing this acid as terminal side chains will not agglutinate cells of *D. pneumoniae* Type II, although this serum will agglutinate cells of *D. pneumoniae* Type III or VIII,[7] even though the latter two types only have *intercatenary* cellobiouronic acid.[8-10] It appears that the immunological specificity attributable to the terminal acid group in S-II does not seem to be very sensitive to the fact that the acid is glycosidically linked to glucose by a β linkage.

Work on the serological inhibition reaction now in progress in collaboration with Dr. M. Heidelberger, might be expected to shed light on this point and will be reported elsewhere.

The synthesis of 6-*O*-α-D-glucopyranuronosyl-D-glucose (isomaltouronic acid), was initiated starting from 6-*O*-[α-D-glucopyranosyl]-β-D-glucopyranose octaacetate (β-isomaltose octaacetate) (**1**) which was obtained from the acid reversion of glucose following the method of Wolfrom and Thompson.[11] It was deacetylated and tritylated at the 6′ position in pyridine solution. Without further isolation, it was then acetylated and the resulting hepta-*O*-acetyl-6′-*O*-tritylisomaltose (**2**) was isolated by chromatography on silica gel in 61.5% yield. The nmr spectrum indicated that **2** was a mixture of α and β anomers, a finding that was expected, as tritylation in pyridine prior to acetylation would cause anomerization. Detritylation of **2** by brief treatment in acetic acid with 1 mol equiv of hydrogen bromide[12] gave 1,2,3,4,2′,3′,4′-hepta-*O*-acetylisomaltose (**3**) in 83% yield. The heptaacetate **3** was then oxidized with potassium permanganate in acetic acid, and the car-

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