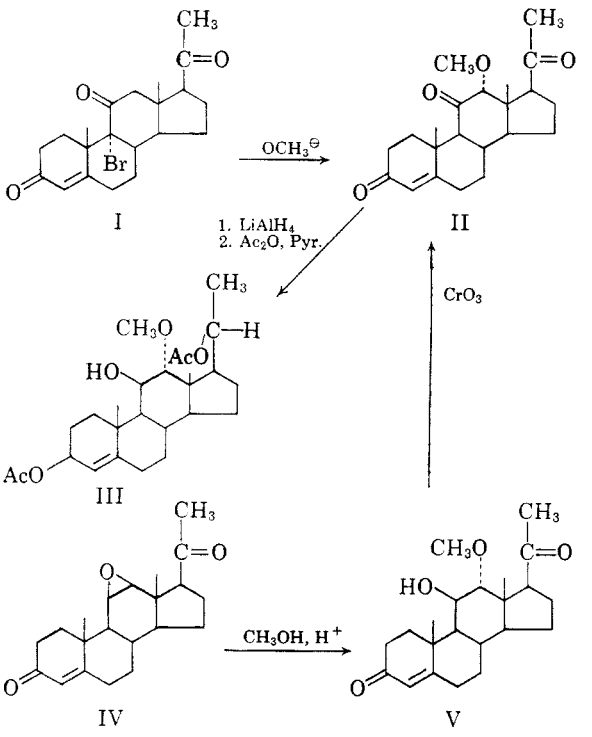

12α-methoxy-11-ketoprogesterone identical with the product of the reaction of I with methoxyl ion. The lithium aluminum reduction product III must then be 12α-methoxy-Δ⁴-pregnene-3β,11β,20β-triol 3,20-diacetate.[10]

EXPERIMENTAL[11]

12α-Methoxy-11-ketoprogesterone (II). (a) *Via 9α-bromo-11 ketoprogesterone* (I). To a stirred suspension of 10 g. of 9α-bromo-11-ketoprogesterone in 300 ml. of methanol which had been flushed with nitrogen, 25 ml. of 2*N* sodium methoxide in methanol was added, and the mixture stirred under nitrogen at room temperature for 2.5 hr. during which time the steroid dissolved. The solution was then neutralized with 10% acetic acid, diluted with 500 ml. of water and extracted three times with 200-ml. portions of chloroform. The chloroform was washed with water and evaporated to dryness *in vacuo*. The residue (9.4 g.) was dissolved in 60 ml. of benzene diluted with 120 ml. of hexane and adsorbed onto 200 g. of Woelm neutral alumina. Elution with benzene-hexane (3:1) or benzene gave a residue on evaporation of the solvent which on crystallization from acetone-hexane gave 3.2 g. of 12α-methoxy-11-ketoprogesterone having a m.p. of 121–122°; $[\alpha]_D^{23}$ +281° (chloroform); λ_{max}^{alc} 235 mμ (ε 19,200); λ_{max}^{Nujol} 2.99, 5.82, 6.02, 6.18, and 6.26 μ.

Anal. Calcd. for $C_{22}H_{30}O_4$: C, 73.71; H, 8.44; OCH_3, 8.65. Found: C, 73.40; H, 8.30; OCH_3, 8.76.

(b) *Via 12α-methoxy-11β-hydroxyprogesterone* (V). To a solution of 100 mg. of 12α-methoxy-11β-hydroxyprogesterone in 4 ml. of reagent grade acetone, 0.13 ml. of an aqueous solution containing 20.0 g. of chromic anhydride and 32.0 g. sulfuric acid per 100 ml. was added dropwise. After stirring at room temperature for 15 min. the excess chromic acid was decomposed by adding a few drops of methanol. The mixture was filtered and washed with acetone. The filtrate was then diluted with 10 ml. of water and extracted with three 5-ml. portions of chloroform. The chloroform was washed with water and evaporated to dryness *in vacuo*. Crystallization from acetone-hexane gave 70 mg. of 12α-methoxy-11-ketoprogesterone (II).

12α-methoxy-Δ⁴-pregnene-3β,11β,20α-triol 3,20-diacetate (III). To a solution of 200 mg. of 12α-methoxy-11-ketoprogesterone in 10 ml. of dry tetrahydrofuran 104 mg. of lithium aluminum hydride was added and the mixture stirred at room temperature for 3 hr. The excess lithium aluminum hydride was decomposed by adding a few drops of ethyl acetate; then 20 ml. each of water and chloroform was added and the mixture acidified with dilute hydrochloric acid. The chloroform was separated, washed with water until neutral and evaporated to dryness *in vacuo*. The residue was dissolved in 3 ml. of dry pyridine and 1 ml. of acetic anhydride was added. After 16 hr. at room temperature ice water was added and the mixture was extracted with chloroform. The chloroform was washed successively with 2*N* hydrochloric acid, 5% sodium bicarbonate, and water and then evaporated to dryness, *in vacuo*. Crystallization of the residue from acetone-hexane gave 100 mg. of 12α-methoxy-Δ⁴-pregnene-3β,-11β,20α-triol 3,20-diacetate having a m.p. of 200–202°; λ_{max}^{Nujol} 2.83, 5.79, 5.86, 6.03 μ.

Anal. Calcd. for $C_{26}H_{40}O_6$ (448.58): C, 69.61; H, 8.99; OCH_3, 6.92. Found: C, 69.16; H, 8.70; OCH_3, 7.32.

12α-Methoxy-11β-hydroxyprogesterone (V). To a suspension of 200 mg. of 11β,12β-oxidoprogesterone in 5 ml. of methanol, 0.1 ml. of 70% perchloric acid was added and the mixture stirred at room temperature for 5 hr. during which time the steroid dissolved. After neutralization with 5% sodium bicarbonate and slow addition of 5 ml. of water, crystals separated. These were filtered, washed with water, and dried to give 172 mg. of 12α-methoxy-11β-hydroxyprogesterone (IV) having a m.p. of 164–165°; $[\alpha]_D^{23}$ + 210° (chloroform); λ_{max}^{alc} 242 mμ (ε 16400); λ_{max}^{Nujol} 2.74, 2.92, 5.88, 6.04, 6.20 μ.

Anal. Calcd. for $C_{22}H_{32}O_4$: C, 73.30; H, 8.95; OCH_3, 8.60. Found: C, 73.30; H, 8.88; OCH_3, 8.92.

Acknowledgment. The authors are indebted to Dr. H. Agahigian for NMR spectra, to Dr. N. Coy for ultraviolet spectra, and to Mr. J. Alicino for microanalyses.

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(10) The assignment of the 20β-configuration to compound III is based on analogy with the work of others [E. P. Oliveto, C. Gerold, and E. B. Hershberg, *J. Am. Chem. Soc.*, **76**, 6111 (1954); **76**, 6113 (1954), E. P. Oliveto and E. B. Hershberg, *J. Am. Chem. Soc.*, **75**, 488 (1953); O. Mancera, H. Ringold, C. Djerassi, G. Rosenkranz, and F. Sondheimer, *J. Am. Chem. Soc.*, **75**, 1286 (1953)] who observed that reduction of 20-ketones by lithium borohydride or sodium borohydride led predominantly to the 20β-isomer.

(11) All melting points were taken in an open capillary and are uncorrected. Ultraviolet spectra were obtained in absolute ethanol.

Sulfur Substitution Compounds of Amino Sugars. IV.[1] Derivatives of 6-Thio-D-glucosamine

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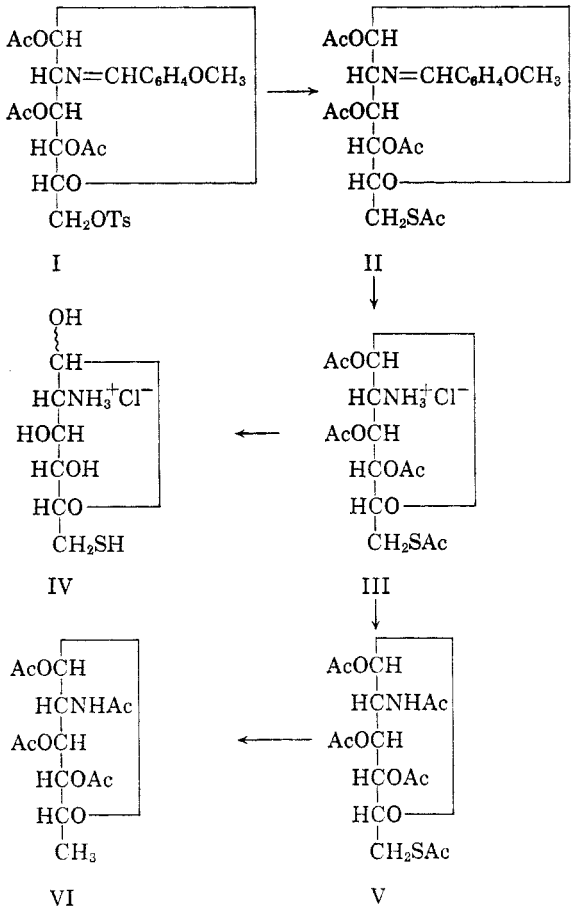
Since completion of our syntheses in the 1-thio-D-glucosamine series,[2,3] we have attempted

(1) Part III, W. Meyer zu Reckendorf and W. A. Bonner, *Proc. Chem. Soc. (London), in press.*

preparation of 6-thio analogs. The ready availability of the 6-tosyl compound I[4] made it desirable to employ the convenient method of Chapman and Owen,[5] who displaced primary tosyl groups by thioacetyl in analogy to the other well known nucleophilic displacements of sulfonates recently summarized by Tipson.[6] The heating of I in refluxing acetone for eight hours with an excess of potassium thioacetate yielded 1,3,4-tri-*O*-acetyl-*S*-acetyl-*N*-*p*-methoxybenzylidene-6-thio-β-D-glucosamine II. Hydrolysis of the Schiff base function was accomplished by heating II in acetone with an excess of hydrochloric acid,[7] affording the hydro-



chloride III. Complete hydrolysis of III under alkaline conditions appeared impossible without concomitant migration of *O*-acetyl to the amino function. Accordingly, we attempted the hydrolysis of III to IV with hydrogen chloride, both in water and in methanol solution, with addition of a trace of 2-mercaptoethanol to prevent oxidation.[8] These attempts, however, proved unsuccessful, yielding only very hygroscopic, nonhomogeneous white powders which defied recrystallization and consistently gave inadequate elemental analyses. Reacetylation of such products, assumed to be mainly IV, yielded what appeared to be mixtures of anomeric acetates. Chromatographic purification of the crude product IV has not been attempted because of the ready oxidizability of its mercaptan function.

The structure proof of III was accomplished by its conversion to the completely acetylated compound V. Desulfurization of the latter with Raney nickel yielded the known[4] 1,3,4-tri-*O*-acetyl-*N*-acetyl-6-deoxy-β-D-glucosamine VI.

EXPERIMENTAL

1,3,4-Tri-O-acetyl-S-acetyl-N-p-methoxybenzylidene-6-thio-β-D-glucosamine (II). 1,3,4-Tri-*O*-acetyl-6-*O*-tosyl-*N*-*p*-methoxybenzylidene-β-D-glucosamine[4] (I; 2.9 g.; 5 mmoles) and potassium thioacetate (640 mg.; 5.5 mmoles) were heated in refluxing acetone (50 ml.) for 8 hr., whereupon the product, 2.4 g. (98%), was precipitated by pouring the mixture into water. After two recrystallizations from ethanol the product had m.p. 168–169° (corr.) and $[\alpha]_D^{25}$ +80.2 (*c*, 1.77; chloroform).

Anal. Calcd. for $C_{22}H_{27}O_9NS$: C, 54.87; H, 5.65; N, 2.91; S, 6.66. Found: C, 54.92; H, 5.60; N, 3.25; S, 6.69.

1,3,4-Tri-O-acetyl-S-acetyl-6-thio-β-D-glucosamine hydrochloride (III). An acetone solution (10 ml.) containing II (480 mg.; 1 mmole) was heated to boiling and 0.1 ml. of concd. hydrochloric acid added. The product precipitated at once. It was washed with ether and recrystallized from glacial acetic acid, yield 350 mg. (88%), m.p. 234–235° dec. (corr.), $[\alpha]_D^{25}$ +38.2 (*c*, 1.1; dimethylsulfoxide).

Anal. Calcd. for $C_{14}H_{22}O_8NSCl$: C, 42.05; H, 5.55; N, 3.50; S, 8.02. Found: C, 42.31; H, 5.35; N, 3.40; S, 8.04.

Attempted acid hydrolysis of III. One hundred milligrams of III and a trace of 2-mercaptoethanol were either heated for 30 min. in 3 ml. of dilute methanolic hydrochloric acid or left in a mixture of 4 ml. of concd. hydrochloric acid and 2 ml. of water at room temperature overnight. The solutions were evaporated to give a colorless syrup which was taken up in absolute ethanol, after which the product was precipitated with absolute ether. The resulting very hygroscopic white powder could not be characterized or further purified.

1,3,4-Tri-O-acetyl-S-acetyl-N-acetyl-6-thio-β-D-glucosamine (V). Compound III (1.5 g.) was dissolved in a mixture of pyridine (15 ml.) and acetic anhydride (5 ml.) at room temperature. After 1 hr. the product was isolated in the usual way and recrystallized twice from 2-propanol, affording 1.0 g. (66%) of colorless needles, m.p. 187–188° (corr.), $[\alpha]_D^{25}$ +7.4° (*c*, 1.08; chloroform).

Anal. Calcd. for $C_{16}H_{23}O_9NS$: C, 47.40; H, 5.72; N, 3.46; S, 7.91. Found: C, 47.20; H, 5.67; N, 3.52; S, 7.94.

1,3,4-Tri-O-acetyl-N-acetyl-6-deoxy-β-D-glucosamine (VI). Compound V (250 mg.) and Raney nickel (2 g.) were heated in refluxing absolute ethanol (10 ml.) for 3 hr. The solution was filtered through Celite and evaporated *in vacuo*, yielding 185 mg. (90%) of a syrup which rapidly crystallized. This was recrystallized twice from ethanol, m.p. 207–208° (corr.), $[\alpha]_D^{25}$ +16.4° (*c*, 0.52; chloroform); lit.[4] m.p. 209–210°; $[\alpha]_D^{20}$ +17.5°.

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New Synthesis of Stilbene and Heterocyclic Stilbene Analogs

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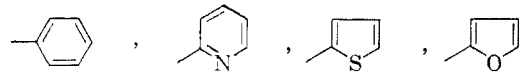
In searching for a more convenient procedure for Wittig's olefin synthesis, Pommer[1] found that the phosphonates obtained from trialkyl phosphites *via* the Michaelis-Arbuzov reaction[2] underwent reaction with aldehydes or ketones in the presence of a strong base to give good yields of olefins. Extensive application of the reaction was made in the carotenoid field. We had applied this reaction to the synthesis of a number of known compounds when Wadsworth and Emmons[3] reported its versatility. Because of the latter publication, we should like to report some of our results in this field.

Stilbene and the heterocyclic analogs, 2-stilbazole, 2-styrylfuran, and 2-styrylthiophene, are obtained in greater than 75% yield by the reaction of diethyl benzylphosphonate with the corresponding aldehyde, using sodium methoxide in dimethylformamide. The exothermic reaction gives the

$$C_6H_5CH_2Br + (C_2H_5O)_3P \longrightarrow C_6H_5CH_2PO(OC_2H_5)_2 + C_2H_5Br$$

$$C_6H_5CH_2PO(OC_2H_5)_2 + ArCHO \xrightarrow[DMF]{NaOCH_3} C_6H_5CH{=}CHAr + (C_2H_5O)_2POONa + CH_3OH$$

Ar = 

trans-olefin in a relatively pure state in 75–85% yields simply by treatment of the reaction mixture with water. The *trans* configuration is assigned to all these compounds on the basis of infrared analyses. A strong absorption at 10.2 to 10.4 μ in all these compounds is characteristic of *trans*-olefins.[4]

The best previous preparations of *trans*-stilbene are Emmons'[3] synthesis from diethyl benzylphosphonate and benzaldehyde with sodium hydride in dimethoxyethane and the Clemmensen reduction of benzoin.[5] *trans*-2-Stilbazole was obtained from 2-picoline and benzaldehyde[6] and from 2-picoline and toluene in acetic anhydride.[7] trans-2-Styrylthiophene[8] and *trans*-2-styrylfuran[9] were prepared by dehydration of the carbinol resulting from the action of benzylmagnesium chloride on the corresponding aldehydes.

The superiority of the present method is shown in Table I.

TABLE I

PREPARATION OF STYRYL DERIVATIVES

$$RCHO + (C_2H_5O)_2P(O)-CH_2C_6H_5 \xrightarrow[DMF]{NaOCH_3} RCH{=}CHC_6H_5 + (C_2H_5O)_2POOH$$

R =	Yield, % Current	Yield, % Previous	M.P. Current[a]	M.P. Previous	Previous References
C_6H_5	85	53–57; 63	126–127[b]	123–124	5 3
	75	57; 51	92.5–93	91	7 6
	77	60	112–113[c]	111	8
	84	12	54–55[d]	49–50	9

[a] Melting points are corrected. [b] Recrystallized from ethanol-ethyl acetate. [c] Recrystallized from ethanol. [d] Recrystallized from methanol.

EXPERIMENTAL

Diethyl benzylphosphonate. Diethyl benzylphosphonate was prepared in 85% yield by the Michaelis-Arbuzov reaction,[2] involving benzyl bromide and triethyl phosphite.

Stilbene and heterocyclic stilbene analogs. Diethyl benzylphosphonate (0.05*M*) and sodium methoxide (10% excess) were combined in dimethylformamide in a three necked flask fitted with a thermometer, drying tube, dropping funnel, and magnetic stirrer. The aromatic or heterocyclic aldehyde (0.05*M*) in dimethylformamide (25–40 ml.) was added dropwise, with stirring and cooling in ice, at such a rate that the reaction temperature was maintained between 30° and 40°; a clear solution resulted. After standing for a short period of time, water was added to the solution, with cooling; the precipitated product was collected on a filter and washed with water. The compounds listed in the Table were prepared by this procedure.

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