chloride to methoxycyclohexylmercuric chloride. Since electrophilic substitution by mercuric chloride on 2-methoxycyclohexylmercury compounds in ether is known to proceed with retention of configuration,[3] the configuration of the final 2-methoxycyclohexylmercuric chloride may be used as a guide to the configuration of the dialkylmercury II.

The 2-methoxycyclohexylmercuric chloride produced from the dialkylmercury II proved to be a mixture of the *trans*- and *cis*-isomers III and IV, quite analogous to the mixture obtained by Wright from the use of hydrazine.[1] The *trans*-isomer III crystallized directly from the reaction mixture in relatively pure form. The *cis*-isomer IV was obtained in pure form by treatment of the residual methoxycyclohexylmercuric chloride with hot acetic acid, taking advantage of the much greater rate of elimination displayed by the *trans*-compound compared to the *cis*-isomer.[3]

Retention of configuration is not complete during conversion of 2-methoxycyclohexylmercuric iodide (I) to dialkylmercury II with sodium stannite, the most likely explanation being that intermediate methoxycyclohexyl free radicals are involved. The *cis*-2-methoxycyclohexylmercuric chloride (IV) represented *ca.* 15% of the product from mercuric chloride cleavage of the dialkylmercury II, less than the figure of 25% which would result if the methoxycyclohexyl radical showed equal preference for *trans*- or *cis*-configurations in the bond-making step of the reaction leading to dialkylmercury II. While some preference for the *trans*-configuration seems indicated, more quantitative interpretation is precluded by the low yield of dialkylmercury II obtained from reduction of *trans*-2-methoxycyclohexylmercuric iodide (I).

EXPERIMENTAL

A 45 g. (0.1 mole) quantity of I was treated with excess sodium stannite by a standard procedure.[5] The resulting crude liquid II, testing negatively for halogen, was obtained in 13% yield. From treatment of this material with an equivalent quantity of mercuric chloride in 40 ml. of ether was obtained an 89% yield of mixed 2-methoxycyclohexylmercuric chlorides III and IV, m.p. 92–106°, m.p. 88–106° after one recrystallization from methanol.

The treatment of the di-(methoxycyclohexyl)mercury(II) with mercuric chloride was repeated using 4.6 g. of II and 2.94 g. of mercuric chloride in *ca.* 75 ml. of technical grade ether. After 3 min. at room temperature, 2.40 g. of a rather pure white solid crystallized out, m.p. 111–112°, mixed m.p. with authentic III 111–112°, mixed m.p. with authentic IV 87–92°. When the ethereal filtrate was evaporated to dryness, 4.94 g. of a solid containing only traces of mercuric chloride was obtained. A 0.78-g. sample of this residue was heated in 3 ml. of glacial acetic acid to 100° for 5 min. Then the resulting solution was poured into 50 ml. of 6*N* sodium hydroxide, mercuric oxide precipitating and the *cis*-mercurial IV being converted to the soluble hydroxide. After removal of the mercuric oxide by centrifugation, the alkaline supernatant was poured into a solution of 2 g. of sodium chloride in 20 ml. of water and acidified with glacial acetic acid. The white solid which precipitated weighed 0.125 g. (11%) and melted at 108.5–111°, mixed m.p. 112–113° with authentic IV, mixed m.p. 88–95° with III. The material gave a negative test[3] for III.

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(5) S. Winstein and T. G. Traylor, *J. Am. Chem. Soc.*, **77**, 3751 (1955); See preparation of di-*s*-butylmercury.

Concerning the Synthesis of Methyl (11-Deoxycorticosteron-21-yl 2,3,4-Tri-*O*-acetyl-β-D-glucosid)uronate

W. WERNER ZORBACH

Received May 26, 1958

In response to a need for a water-soluble derivative of 11-deoxycorticosterone (I), the preparation of a 21-glucosiduronic acid was undertaken. The preparation of the 21-glucoside of I has been previously reported,[1] as well as the 21-glucosides of both cortisone and 17α-hydroxy-11-deoxycorticosterone[2]; however, the solubility in water of these derivatives is limited.

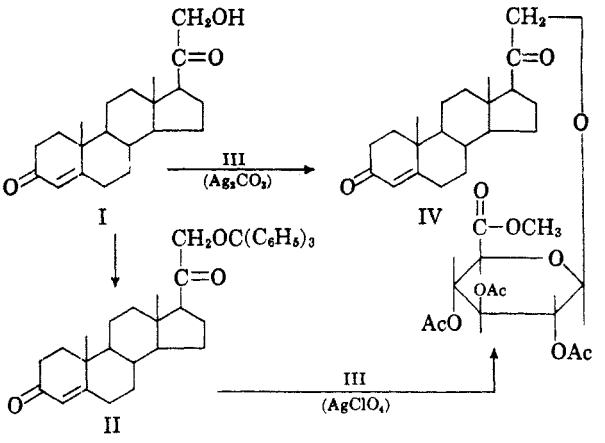
Particularly significant is the coupling of methyl 2,3,4-tri-*O*-acetyl-1-bromo-1-deoxy-α-D-glucuronate (III) with 21-acetoxy-3α,17α-dihydroxypregnane-11,20-dione.[3] The protecting groups were not removed, however, and the glucosiduronate thus secured was compared directly with the methylated and fully acetylated derivative of the glucosiduronic acid recovered from the urine after administration of 3α,17α,21-trihydroxypregnane-11,20-dione. This work strongly supports the general belief that conjugation of glucuronic acid with metabolic reduction products of corticoids, as well as of certain steroid hormones, takes place at C(3). Reported also is the synthesis of the 3,21-bis(methyl 2,3,4-tri-*O*-acetyl-β-D-glucosiduronate) of 3β,17α,-21-trihydroxy*allo*pregnan-20-one.[4] Both of these, however, are conjugates of inactive corticoids. The preparation of a 21-glucosiduronic acid of 11-deoxycorticosterone (I) would be of especial interest for I is an active corticoid; further, the attachment of the glucuronic acid would be at a point other than C(3). Such a derivative might, therefore, display interesting biological properties.

(1) (a) W. S. Johnson, *J. Am. Chem. Soc.*, **63**, (1941); (b) K. Miescher, W. H. Fischer, and C. Meystre, *Helv. Chim. Acta*, **25**, 40 (1942).

(2) C. Meystre and K. Miescher, *Helv. Chim. Acta*, **34**, 2286 (1951).

(3) J. J. Schneider, M. L. Luobart, P. Levitan, and S. Lieberman, *J. Am. Chem. Soc.*, **77**, 4184 (1955).

(4) H. H. Wotiz, J. H. Leftin, E. Smakula, and N. N. Lichtin, Abstracts, Div. Biol. Chem., American Chemical Society 131 National Meeting, April 1957, p. 58C.



Treatment of 11-deoxycorticosterone with methyl 2,3,4-tri-*O*-acetyl-1-bromo-1-deoxy-α-D-glucuronate (III) under conditions essentially the same as described by Meystre and Miescher[2] in their modification of the Königs-Knorr synthesis gave 52% of methyl (11-deoxycorticosteron-21-yl 2,3,4-tri-*O*-acetyl-β-D-glucosid)uronate (IV). Attempts, however, to secure a crystalline 21-glucosiduronic acid of I were unsuccessful. Removal of the blocking groups from the sugar moiety of IV by various hydrolytic measures always resulted in a hygroscopic glass-like material, which could not be brought to a state of sufficient purity for a satisfactory analysis. Attempts to determine the neutral equivalent of the amorphous material resulted in values which deviated 10–15% from the calculated value. The substance gave an acid reaction, was extremely soluble in water, and reacted with diazomethane to give a methylated derivative which was likewise amorphous.

An alternate route to IV was investigated in which application of an ingenious oligosaccharide synthesis, recently described by Bredereck and coworkers,[5] was made. Thus, by converting I to 21-trityloxyprogesterone (II) and allowing the latter to react with molar equivalents of III and of silver perchlorate at 0°, IV was obtained and subsequently identified by ultraviolet and infrared spectral comparisons. Although this reaction was virtually instantaneous, yields were of a very low order. In spite of this, the latter method may have some value, particularly in cases where heat-sensitive acylglycosyl halides are involved. Extension of this work relative to the preparation of the 21-glucosiduronic acid derivatives of other active corticoids is in progress in this laboratory.

EXPERIMENTAL

All melting points were determined using a Kofler hot-stage.

Methyl (11-deoxycorticosteron-21-yl 2,3,4-tri-O-acetyl-β-D-glucosid) uronate (IV) *via the Königs-Knorr Syntheses.* To a magnetically stirred solution of 500 mg. (1.5 mmole) of 11-deoxycorticosterone (I) in 80 ml. of anhydrous carbon tetrachloride was added 1450 mg. of dry silver carbonate. By heating the flask and contents in an oil bath, approximately one-half of the solvent was caused to distill over at a moderate rate. The flask was then fitted with a graduated dropping funnel which contained a solution of 1500 mg. of methyl 2,3,4-tri-*O*-acetyl-1-bromo-1-deoxy-α-D-glucuronate (III) in 40 ml. of anhydrous carbon tetrachloride. This was added drop-wise to the stirring mixture in the flask over a period of 1 hr., during which time the solvent from the reaction flask was permitted to distill over at the same rate. Finally, the temperature of the bath was adjusted so that an additional 20 ml. of the solvent distilled over during a period of 40 min.

To the material remaining in the flask was added 20 ml. of acetone and a small amount of Darco. The solution was filtered by suction and evaporated *in vacuo* at 40°, yielding a sirupy residue which was triturated with ether-ethanol (1-1). The crude crystalline material thus obtained was recrystallized three times from absolute ethanol giving 511 mg. (52%) of material melting at 201–207.5°. Repeated crystallization from absolute ethanol gave pure IV, m.p. 205–207.5°, $[\alpha]_D^{20°}$ +68° (*c* 2.0, $CHCl_3$), λ_{max}^{alc} 240 mμ (4.2).

Orientation at the glycosidic linkage in IV was determined by the method of molecular rotational additivities according to Klyne.[6] Calcd. for [M] [11-deoxycorticosterone (I) + [M] [methyl (methyl 2,3,4-tri-*O*-acetyl-α-D-glucosid) uronate][7a]: +587° + 605° = +1192°. Calcd. for [M] (I) + [M] [methyl (methyl 2,3,4-tri-*O*-acetyl-β-D-glucosid) uronate][7b] +587° − 101° = +486°. Found for [M] (IV): + 439°. The glycosidic linkage in IV has, therefore, the β configuration.

Anal. Calcd. for $C_{34}H_{46}O_{12}$: C, 63.18; H, 7.13. Found: C, 62.89; H, 7.26.

21-Trityloxyprogesterone (II). To a solution of 990 mg. (3.0 mmole) of 11-deoxycorticosterone (I) in 3.0 ml. of anhydrous pyridine was added 921 mg. of trityl chloride. The solution was warmed on a steam bath (under exclusion of moisture) for 3 hr., then extracted successively with *N* sulfuric acid, dilute sodium bicarbonate, and water. The dried extract was evaporated *in vacuo* at 40°, the oily residue triturated with absolute ethanol, and the resulting crystalline material recrystallized once from the same solvent, yielding 1161 mg. (67%) of material melting at 168–172°. Repeated recrystallization from dry 2-propanol gave analytically pure 21-trityloxyprogesterone (II), m.p. 170–173°, $[\alpha]_D^{20°}$ +90.2°.

Anal. Calcd. for $C_{46}H_{44}O_5$: C, 83.87; H, 7.74. Found: C, 83.57; H, 7.89.

The conversion of 21-trityloxyprogesterone (II) to IV. To a solution of 191 mg. (0.33 mmole) of II and 69 mg. (0.33 mmole) of silver perchlorate in 4 ml. of pure, anhydrous nitromethane previously cooled to 0°, was added a solution of 132 mg. (0.33 mmole) of the bromide III in the same solvent. The mixture was filtered immediately to remove insoluble by-products, the filtrate dissolved in methylene chloride, and extracted rapidly with aqueous sodium bicarbonate. After drying over sodium sulfate, the extract was evaporated *in vacuo* at 40° and the oily residue dissolved in a small amount of absolute ethanol. By refrigerating for 24 hr., 11 mg. (5%) of IV was secured which, when recrystallized twice from absolute ethanol, melted at 205.5–208°, λ_{max}^{alc} 240 mμ (4.2). When admixed with a specimen obtained in the foregoing preparation, no depression in the melting point was observed. The ultraviolet and infrared spectra of IV prepared by the two routes were identical in all respects.

(5) H. Bredereck, A. Wagner, and G. Faber, *Angew. Chem.*, 69, 438 (1957).

(6) W. Klyne, Proc. Biochem. Soc., 288 Meet., *Biochem. J.*, 47, x li (1950).

(7) E. Hardegger and D. Spitz, *Helv. Chim. Acta*, (a) 32, 2165 (1949); (b) 33, 337 (1950).

Acknowledgments. The author is indebted to Mr. Harold K. Miller and Mrs. Anne H. Wright for preparing the infrared and ultraviolet spectra, respectively. For the combustion analyses, he wishes to thank Miss Paula M. Parisius of this Institute's Microanalytical Laboratory, under the direction of Dr. W. C. Alford. He is especially grateful to Dr. Erich Mosettig for his interest and encouragement during the course of this investigation.

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Desulfurization of Thiiranes with Triethyl Phosphite

ROBERT D. SCHUETZ AND RICHARD L. JACOBS[1]

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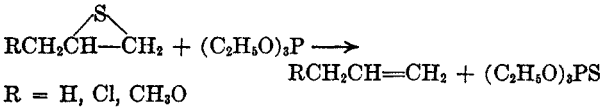
Recently Scott has reported[2] that the reaction of ethylene oxides with triethyl phosphite, results in the reduction of the epoxide to the corresponding olefin and oxidation of the phosphite to phosphate. For example, when equivalent amounts of triethyl phosphite and either ethylene or propylene oxide were heated in a stainless steel bomb at 150–175° for several hours, high yields of the corresponding olefin and triethyl phosphate were obtained.

In the course of recent investigations in these laboratories concerned with the synthesis and ring opening reactions of unsymmetrically substituted thiacycloalkanes, it was observed that heating an equimolar mixture of triethyl phosphite and a thiirane at its reflux temperature for a short period of time resulted in the formation of triethyl thionophosphate with the simultaneous conversion of the thiirane to its corresponding unsaturated compound.

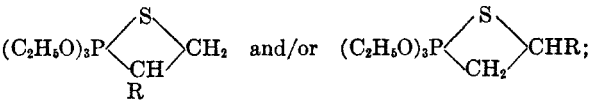


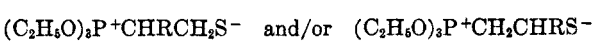
Preliminary results indicate that a wide variety of thiiranes are susceptible to this desulfurization process. In each instance, the reaction yields, within experimental limits, quantitative amounts of triethyl thionophosphate and the unsaturate under much milder conditions than those employed with the oxygen analogs.

(1) Abstracted in part from the doctoral thesis of R. L. Jacobs.

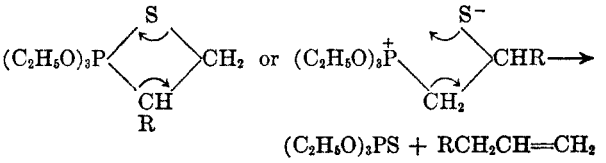
(2) C. B. Scott, *J. Org. Chem.*, **22**, 1118 (1957).

With regard to the reaction of thiiranes with triethyl phosphite, a mechanistic interpretation similar to that offered by Scott[2] may be applicable. Thus, a nucleophilic attack by phosphite on either ring carbon atom could produce intermediates such as the following

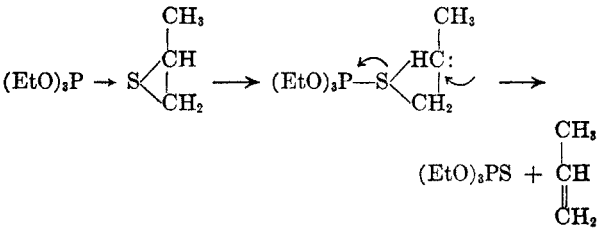




A subsequent rearrangement of such intermediates could then account for the observed products



However, while the above mechanism would satisfactorily account for the observed products, the recent work of Bordwell[3] and collaborators on 1,2 elimination reactions of thiacyclopropanes with organolithium compounds, which give rise to olefins, would suggest an alternative mechanism in which direct attack by phosphite on sulfur occurs. This mechanism can be formulated as,



The first step in the reaction is facilitated by coordination of sulfur with phosphite and breaking of the carbon-sulfur bond. This yields a pair of electrons which could initiate a 1,2-elimination reaction resulting in the simultaneous formation of olefin and thionophosphite. It was found that the ethylene sulfides react readily under the mild conditions described in the experimental section while the corresponding ethylene oxides gave little or no reaction under the same experimental conditions.

The present work extends the list[4] of types of organosulfur compounds that are desulfurized by triethyl phosphite.

EXPERIMENTAL

Materials. Propylene oxide and epichlorohydrin were obtained from commercial sources and were used as received.

(3) F. G. Bordwell, H. M. Anderson, and B. M. Pitt, *J. Am. Chem. Soc.*, **76**, 1082 (1954).

(4) (a) H. I. Jacobsen, R. G. Harvey, and E. V. Jensen, *J. Am. Chem. Soc.*, **77**, 6064 (1955); (b) F. W. Hoffman, R. J. Ess, T. C. Simmons, and R. S. Hanzel, *J. Am. Chem. Soc.*, **78**, 6414 (1956); (c) C. Walling and R. Rabinowitz, *J. Am. Chem. Soc.*, **79**, 5326 (1957).