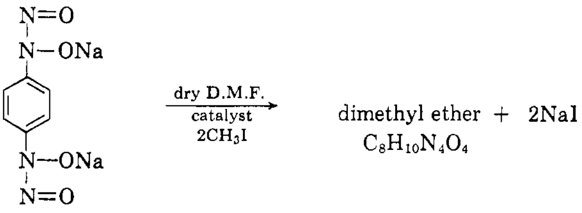
alkylation of phenols has been reported.[2] It has been shown that if the quaternary ammonium salt is insoluble, little effect is noted; whereas, when a soluble quaternary ammonium salt is used, a marked increase in rate is observed. Because of the extremely low solubility of the disodium *N*,*N*′-dinitroso-*p*-phenylenedihydroxylamine, alkylation with methyl iodide is insignificant after three days at room temperature. In the presence of the soluble quaternary salt, however, the alkylation proceeds and the yield of product is improved. It is believed that an equilibrium is established between disodium *N*,*N*′-dinitroso-*p*-phenylenedihydroxylamine and the quaternary ammonium salt to establish a soluble intermediate which is then methylated.

To establish the possible identity of the intermediate involved, dipiperidine-*N*,*N*′-dinitroso-*p*-phenylenedihydroxylamine was methylated with and without the catalyst under identical conditions. With the increased soubility of the dipiperidine salt over the disodium salt, the reaction in dry dimethylformamide proceeds. However, if the soluble quaternary ammonium salt is introduced in the above reaction, the methylation takes place much more rapidly and a higher yield of product is obtained.

Because of reasons previously described,[1] the exact structure of the diether is unknown.



I

EXPERIMENTAL

Dimethyl ether of I. Three grams of the disodium *p*-phenylene-*N*,*N*′-dinitrosodihydroxylamine (I), 3 g. of methyl iodide, and 6 g. of dry triethylallylammonium bromide were introduced into 30 ml. of dry dimethylformamide.

The reaction mixture was let stand at room temperature for 24 hr. under desiccant and stirring. The reaction mixture was diluted with water and extracted with chloroform. The chloroform was removed and a small amount of ether added to facilitate crystallization of the crude product. The product was filtered and washed with cold ether and cold acetone. The product was recrystallized from ethanol. Yield: 1.3 g. (68%); m.p., 205–207° uncorrected.

Dimethyl ethers from the dipiperidine salt. The procedure was the same as above except that the reaction was carried out in the absence of the quaternary ammonium salt catalyst. Yield: 0.44 g. (24.1%); m.p., 205–207° uncorrected.

Dimethyl ether of the dipiperidine salt. The reaction was carried out with the quaternary ammonium salt catalyst and a 3-hr. reaction time. Yield: 1.0 g. (53.6%); m.p., 204–206° uncorrected.

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The *gem*-Dimethyl Effect in Thiacyclodecanes

PAUL FRIEDMAN AND PAUL ALLEN, JR.

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We would like to report the synthesis of two new cyclic sulfides, thiacyclodecane and 6,6-dimethylthiacyclodecane. While thiacyclooctane and thiacyclononane have been prepared in yields of 34% and 6.6%, respectively,[1] the next higher cyclic sulfide to have been prepared was thiacyclotridecane,[2] the hiatus between the nine- and thirteen-membered rings emphasizing the difficulties usually experienced in the synthesis of medium ring compounds.

To determine if the "*gem*-dimethyl effect"[3] would counteract the usual "medium-ring effects"[4] in a ring closure proceeding by a nucleophilic displacement by sulfide ion on a saturated carbon atom, parallel syntheses of the sulfides reported above were carried out.

In view of the comparatively large yield of the substituted compound we conclude that the *gem*-dimethyl effect is operative in this reaction. The preparation of the medium ring homologs of 6,6-dimethylthiacyclodecane is now in progress and the results should further test the above conclusion.

EXPERIMENTAL

5,5-Dimethyl-1,9-nonanediol. A solution of 9.0 g. (0.033 mole) of diethyl-δ_1,δ-dimethyl azealate[5] in 10 ml. of anhydrous ether was added dropwise to a well stirred mixture of 1.9 g. (0.05 mole) of lithium aluminum hydride and 100 ml. of anhydrous ether. The mixture was stirred for 90 min. after the addition was complete, and 10 ml. of water was cautiously added. After 20 min. stirring the ether solution was filtered from the white precipitate which was then triturated with an additional 50 ml. of ether. The combined ether solutions, after drying yielded 5.4 g. (87.2%) of the diol, b.p. 118–119° (1 mm.), $n^{21.5}_D$ 1.4625.

Anal. Calcd. for $C_{11}H_{24}O_2$: C, 70.16; H, 12.84. Found: C, 70.16; H, 12.92.

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(1) A. Muller, E. Funder-Fritzche, W. Konar, and E. Rintersbacher-Wlasak, *Monatsh.*, **84**, 1206 (1953).

(2) A. Muller and A. F. Schultz, *Ber.*, **71**, 692 (1938).

(3) N. L. Allinger and V. Zalkow, *J. Org. Chem.*, **25**, 701 (1960); E. L. Eliel in *Steric Effects in Organic Chemistry*, John Wiley and Sons, Inc., New York, 1956, p. 118–120.

(4) V. Prelog, *J. Chem. Soc.*, 420 (1950); N. L. Allinger and S. Greenberg, *J. Am. Chem. Soc.*, **81**, 5737 (1959).

(5) This ester was prepared by the bis-homologation procedure of Blomquist [A. T. Blomquist, E. S. Wheeler, and Y. Chu, *J. Am. Chem. Soc.*, **77**, 6307 (1955)].

1,9-Dibromo-5,5-dimethylnonane.[6] To 9.0 g. (0.044 mole) of phosphorus tribromide at −10°, 5.0 g. (0.026 mole) of 5,5-dimethyl-1,9-nonanediol was added with stirring over a 2-hr. period. Stirring was maintained as the mixture was allowed to warm to room temperature and then heated at 80° overnight. The cooled mixture was treated with 10 ml. of water, and the lower organic layer was separated. The aqueous layer was extracted with methylene chloride. The methylene chloride extract, combined with the organic layer was washed with dilute sodium bicarbonate and dried. Distillation yielded 6.7 g. (80.1%) of the dibromide b.p. 102° (0.5 mm.) $n^{22.5}\text{D}$ 1.4952.

Anal. Calcd. for $C_{11}H_{22}Br_2$: C, 42.05; H, 7.06. Found: C, 42.38; H, 7.29.

6,6-Dimethylthiacyclodecane.[7] A solution of 3.14 g. (0.01 mole) of 1,9-dibromo-5,5-dimethylnonane in 1 l. of anhydrous ethanol was added by a Hershberg dropping funnel through a high dilution adapter[8] to 2.5 l. of refluxing anhydrous ethanol with vigorous stirring over a 34-hr. period. Simultaneously a solution of 1.56 g. (0.02 mole) of sodium sulfide in 100 ml. of anhydrous ethanol was added through a 6-in. Vigreux column over the same period of time by means of an infusion pump.[9] After the additions were complete, the solution was refluxed with stirring for an additional hour and almost all of the ethanol was distilled from the reaction mixture. The residue was steam distilled and the distillate was treated with aqueous mercuric chloride. The white complex was collected, washed with water, and steam distilled. Extraction of the distillate with ether, drying, and distillate of the residue yielded 0.64 g. (34.5%) of the sulfide, b.p. 255°/760 mm., 140–5°/20 mm., $n^{26}\text{D}$ 1.5035.

Anal. Calcd. for $C_{11}H_{22}S$: C, 70.89; H, 11.82; S, 17.24. Found: C, 70.48; H, 11.78; S, 17.68.

Thiacyclodecane. Following the procedure for 6,6-dimethylthiacyclodecane, 2.86 g. (0.01 mole) of 1,9-dibromononane (Matheson, Coleman and Bell) yielded 91 mg. (5.7%) of thiacyclodecane[10] $n^{23.6}\text{D}$ 1.5178.

Anal. Calcd. for $C_9H_{18}S$: C, 68.35; H, 11.39; S, 20.26. Found: C, 68.40; H, 11.38; S, 20.27.

Acknowledgment. We are indebted to the National Institutes of Health, Grant A-3649 (ClSl), for support of this work.

Department of Chemistry and Chemical Engineering
Stevens Institute of Technology
Hoboken, N. J.

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(6) A. T. Blomquist and J. Verdol, *J. Am. Chem. Soc.*, **77**, 1806 (1955).

(7) The procedure used is a modification of the method of Muller (see ref. 1).

(8) N. J. Leonard and R. C. Sentz, *J. Am. Chem. Soc.*, **74**, 1704, (1952).

(9) Harvard Apparatus Corp., Dover, Mass., Model 600,-000.

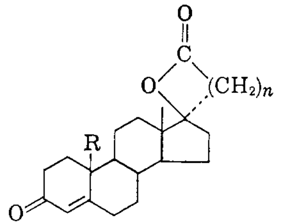
(10) A duplicate run resulted in a 5.2% yield of thiocyclodecane.

Synthesis of 17α-Hydroxy-21-carboxypregn-4-en-3-one Lactone

H.-J. Hess

Received September 28, 1961

Spirolactones of the general formula I have received much attention because of their electrolyte regulating activity, antagonistic to desoxycorticosterone acetate and to aldosterone.[1a–d] More recently, it was shown that alkali salts[2] of the corresponding hydroxy acids exhibit activity of equal potency.



I

R = H, CH_3; $n = 2, 3$

It was of interest to investigate the significance of the stereochemistry at C-17 and a typical spirolactone isomer (VI), with the opposite configuration at C-17, was therefore synthesized.

Addition of acetic acid to 21-methylene-17α-hydroxypregnenolone[3] (II) at 60° in the presence of sodium acetate resulted in the formation of III and subsequent acetylation with acetic anhydride in pyridine gave the diacetate IIIa. Reduction of the C-20 ketone function with sodium borohydride in methanol furnished the diacetylated tetrol IV. This material, which appeared to be homogeneous,[4] was converted directly to the methane sulfonate IVa with methanesulfonyl chloride in pyridine. Subsequent reduction of IVa with excess lithium aluminum hydride gave 3β,17α-dihydroxy-21-hydroxymethyl-pregn-5-ene (V). Protection of the double bond in V with bromine permitted simultaneous oxidation of the 3-alcohol[5] and the primary alcohol in the side chain with chromic acid in acetic acid. Elimination of bromine with zinc and isomerization with hydrochloric acid gave the α,β-unsaturated ketone. Under these conditions cyclization of the γ-hydroxy acid to the lactone VI occurred spontaneously. Isolated as a by-product, the partially oxidized spirolactone VII was identified by its infrared spectrum, analysis, and absence of absorption in the ultraviolet spectrum and by further oxidation to VI with chromic acid in ace-

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(2) C. M. Kagawa and E. A. Brown, *Proc. Soc. Exptl. Biol. Med.*, **105**, 648 (1960).

(3) H.-J. Hess, S. K. Figdor, G. M. K. Hughes, Rex Pinson, Jr., and W. T. Moreland, Abstracts 138th Meeting, ACS, 1960, p. 39P.

(4) The possibility, however, that it consisted of a mixture of epimeric alcohols can not be excluded. In view of the fact that this asymmetric center was to be eliminated at a later stage, no attempts for separation or purification were undertaken.

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