

and the solvent was removed by evaporation. The activity was measured in a Tracerlab internal flow Geiger counter. As the concentration of nitrogenous base in each aliquot was known from optical density measurements, specific activity could be calculated.

Purity Criteria.—The fractions of each base were found to be satisfactorily pure as judged from the ratio of the optical densities at two selected wave lengths and by the ratio of radioactivity to optical density.

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Chemical Studies with 11-Oxygenated Steroids. V. $3\alpha,20\beta$ -Dihydroxypregnan-11-one 11-Ethylene Ketal¹

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It is well established that the 11-keto function frequently found in steroids fails to react with the usual carbonyl reagents.² Catalytic or chemical reduction to the 11-hydroxyl function^{2,3} and participation in the Wolff-Kishner reduction⁴ are the only recorded reactions of the 11-keto moiety.

Various investigators have reported the selective preparation of cyclic ketals at other positions in the molecule leaving the 11-keto function intact.⁵ It was found in these laboratories that prolonged boiling of $3\alpha,20\beta$ -dihydroxypregnan-11-one with ethylene glycol in benzene solution in the presence of *p*-toluenesulfonic acid gave the 11-ketal in 50% yield. This compound shows strong hydroxyl absorption and complete lack of carbonyl absorption in its infrared absorption spectrum. Acidic hydrolysis gave 85% yield of the starting $3\alpha,20\beta$ -dihydroxypregnan-11-one which was identified by mixed melting point and infrared data.

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Experimental⁶

$3\alpha,20\beta$ -Dihydroxypregnan-11-one 11-Ethylene Ketal.—A mixture of 4.0 g. of $3\alpha,20\beta$ -dihydroxypregnan-11-one,⁷ 12 ml. of ethylene glycol, 100 mg. of *p*-toluenesulfonic acid monohydrate and 150 ml. of benzene was stirred and heated under reflux for 72 hours. The water formed in the reaction was codistilled with the benzene and removed in a water

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(2) L. F. Fieser and M. Fieser, "Natural Products Related to Phenanthrene," 3rd Edition, Reinhold Publishing Corp., New York, N. Y., 1949, pp. 409-410.

(3) L. H. Sarett, M. Feurer and K. Folkers, *THIS JOURNAL*, **73**, 1777 (1951); N. L. Wendler, Huang-Minlon and M. Tishler, *ibid.*, **73**, 3818 (1951); H. Heyman and L. F. Fieser, *ibid.*, **73**, 5252 (1951); H. L. Herzog, M. A. Jevnik and E. B. Hershberg, *ibid.*, **75**, 269 (1953); F. Sondheimer, O. Mancera, G. Rosenkranz and C. Djerassi, *ibid.*, **75**, 1282 (1953).

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(6) Melting points are uncorrected.

(7) L. H. Sarett, *THIS JOURNAL*, **70**, 1690 (1948).

trap. The cooled solution was filtered to give, after washing with methylene dichloride, 2.27 g. (50.2% yield) of crystals, m.p. 250-255°. The benzene-ethylene glycol solution, after washing with water and concentrating, gave an additional 1.51 g. of crystals, m.p. 208-216°. The 2.27 g. of ketal was recrystallized from methanol to give 1.58 g., m.p. 257-259°. The infrared absorption spectrum of this material showed no carbonyl absorption in the 6 μ region.

Anal. Calcd. for $C_{23}H_{38}O_4$: C, 72.97; H, 10.12. Found: C, 72.92, 73.00; H, 10.24, 10.22.

Hydrolysis of $3\alpha,20\beta$ -Dihydroxypregnan-11-one 11-Ethylene Ketal.—A solution of 200 mg. of the 11-ketal in 20 ml. of acetone and 2 ml. of water containing 2 drops of concentrated sulfuric acid was heated under reflux for 2 hours. The acetone was distilled under vacuum, water added and the product filtered. It weighed 150 mg. (84.6% yield), m.p. 231-235°. After recrystallization from benzene-methanol there was obtained 130 mg., m.p. 235-237°. This material gave no melting point depression with $3\alpha,20\beta$ -dihydroxypregnan-11-one. Its infrared absorption spectrum was identical with the starting ketone.

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Deuterium-Hydrogen Exchange in the *para* Position of Phenyl Alkyl Ethers¹

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The influence of groups in the aromatic nucleus on chemical reactivity at a particular position has been the subject of many experimental and theoretical studies. The present study constitutes an investigation of the rates of deuterium-hydrogen exchange occurring in the *ortho* and the *para* positions of anisole and in the *para* positions of phenetole, phenyl *n*-propyl ether and phenyl isopropyl ether. These exchange reactions were conducted in acid solution at a temperature of 100°.

The deuterium labeled aromatic ethers were prepared from the corresponding bromo ethers by first converting these compounds to their lithium derivatives and then replacing the metal by deuterium with heavy water. These labeled aromatic ethers after dilution with unlabeled material were dissolved in glacial acetic acid containing sulfuric acid and the time required for one-half of the deuterium to be replaced by hydrogen was determined. The labeled aromatic ethers, held at constant temperature for definite time intervals, were isolated from solution by treatment with aqueous sodium hydroxide. These samples were then burned in a stream of oxygen and the water of combustion, after purification, was analyzed for deuterium. This analysis was accomplished by the falling drop procedure.³

The half-life of deuterium in the case of *para*-labeled anisole at 100° in a solution containing the aromatic ether (0.01 mole), glacial acetic acid (0.05 mole) and sulfuric acid (0.001 mole) was found to be 39 minutes ($k = 3.0 \times 10^{-4}$ sec.⁻¹), and the half-life of deuterium in the case of *ortho*-labeled anisole under similar conditions was found to be 75 minutes ($k = 1.5 \times 10^{-4}$ sec.⁻¹). A comparison of the exchange rates of *o*-deuteroanisole with the

(1) From the Ph.D. Thesis of John T. Day, September, 1951.

(2) Abbott Laboratories Fellow, 1950-1951.

(3) I. Kirshenbaum, "Physical Properties and Analysis of Heavy Water," McGraw-Hill Book Co., Inc., New York, N. Y., 1951.

para isomer (1.0) gave the following ratios: *ortho/para* 0.52 at 100° and 0.33 at 80°. These findings relating orientation to temperature are at least qualitatively in agreement with experience, since lowered temperatures usually favor higher percentages of the *para* isomer upon substitution in the case of phenols and their derivatives.

The replacement of deuterium with hydrogen in an acidic medium is an electrophilic substitution. The usual order of intensity of the inductive effects of the alkyl groups involved in the present study is $\text{CH}_3 < \text{CH}_3\text{CH}_2 \sim \text{CH}_3\text{CH}_2\text{CH}_2 < (\text{CH}_3)_2\text{CH}$. Thus the release of electrons by the isopropyl group is more facile than in the case of the methyl group; consequently, the rate of deuterium-hydrogen exchange should be more rapid in the *para* position of phenyl isopropyl ether than in the corresponding position of anisole. This has been found to be the case. The influence of the alkyl groups as manifested by the comparative exchange rates at 100° proved to be methyl (1.00), ethyl (1.34), *n*-propyl (1.37) and isopropyl (2.60). These relative rates for exchange are in agreement with the order of influence of these groups in the case of other electrophilic substitutions in aromatic ethers.⁴

Experimental

***p*-Deuterophenyl Alkyl Ethers.**—These ethers were prepared from the *p*-bromophenyl alkyl ethers by the following procedure. A solution of the *p*-bromophenyl alkyl ether (0.1 mole) in anhydrous ether (75 ml.) was added to an excess of finely divided lithium (2.0 g.) in anhydrous ether (80 ml.). The intermediate organolithium compound formed in a short time at the boiling point of ether. Deuteration was accomplished by the cautious addition of heavy water (usually 99.75% D₂O, 4 g.). The mixture then was filtered to remove the lithium bromide and lithium hydroxide. After the ether was separated by distillation, the residue was distilled at reduced pressure in order to obtain the *p*-deuterophenyl alkyl ether. The *p*-deuterophenyl alkyl ether was then diluted with unlabeled ether.

Exchange Studies.—The calculated amount of the *p*-deuterophenyl alkyl ether was weighed out and mixed with the calculated amount of stock solution. The stock solution contained sulfuric acid dissolved in glacial acetic acid. The proportions used were 0.01 mole of *p*-deuterophenyl alkyl ether, 0.001 mole of concd. sulfuric acid and 0.05 mole of glacial acetic acid. Small (6 mm.) exchange tubes were then filled with this solution, sealed and placed in a constant temperature bath. The first tube was withdrawn from the bath after an elapsed time of two minutes. This was considered to be the starting time of the exchange reaction. The remaining tubes were withdrawn at predetermined time intervals. The sample was then removed from the exchange tube and the phenyl ether was separated by adding dilute sodium hydroxide. The two immiscible layers were separated. Treatment with base was repeated and the layers were again separated after having been subjected to centrifugation. A sample of the organic layer was then combusted at 730° in a stream of oxygen. The water of combustion (*ca.* 70 mg.) was condensed in a Dry Ice trap. After heating to the boiling point over a few milligrams of potassium permanganate and calcium oxide, the water is transferred by distillation under reduced pressure to a small trap which could be removed from the apparatus and capped.

Deuterium Analyses.—A micropipet of construction similar to that of the Gilmont Ultramicroburet was mounted on a heavy stand by means of a rack and pinion so that it could be raised and lowered easily. The pipet, in raised position, was filled by submerging the tip into the water sample to be analyzed. The micrometer was turned to expel a droplet of

mercury; the complete removal of air from the tip therefore was assured. The micrometer was then backed up to fill the pipet with the required amount of water. The tip of the pipet was then removed from the water sample and the micrometer was backed up about one-half turn to allow air to enter the end (*ca.* 5 mm.) of the tip. The pipet was then lowered by means of the rack and pinion so that the tip was well below the surface of the liquid in the density measuring tube. The micrometer was then turned slowly and a small bubble of air was formed in the liquid. At the moment the air bubble detached itself from the tip, a micrometer reading was taken. The micrometer was then turned two complete revolutions to form a drop of water which remained attached to the tip of the pipet. The pipet was slowly raised by means of the rack and pinion and the drop was detached. It was found that this procedure gave results which were highly reproducible. The density measuring tube containing the immiscible liquid, *o*-fluorotoluene, was 9 cm. × 25 cm. and two lines, one 5 cm. and the other 20 cm. from the bottom were engraved on the tube. The time of descent of the drop of water between these two lines was measured with a stopwatch. The tube containing the *o*-fluorotoluene was supported in a carefully regulated thermostat. A number of standard solutions of heavy water were used for calibration purposes.

Results.—The D/(D + H) ratio was calculated from the time of descent of the water drop and the calibration curve. The ratio which resulted in the case of the exchange tube removed from the bath at the end of two minutes was taken as the D/(D + H) ratio at zero time.

TABLE I
p-DEUTEROANISOLE

| Time, min. | [D/(D + H) _{obsd.}] | $\frac{[\text{D}/(\text{D} + \text{H})]_t}{[\text{D}/(\text{D} + \text{H})]_{t_0}} \times 100$ |
|--|-------------------------------|--|
| Half-life 39 min., $k = 3.0 \times 10^{-4}$ sec. ⁻¹ , temp. 100° | | |
| 0 | 0.00774 | 100 |
| 10 | .00658 | 85 |
| 20 | .00548 | 71 |
| 30 | .00457 | 59 |
| 40 | .00382 | 49 |
| 50 | .00330 | 43 |
| Half-life 133 min., $k = 0.87 \times 10^{-4}$ sec. ⁻¹ , temp. 80° | | |
| 0 | 0.00774 | 100 |
| 20 | .00695 | 90 |
| 40 | .00627 | 81 |
| 60 | .00546 | 73 |
| Half-life 39 min., $k = 3.0 \times 10^{-4}$ sec. ⁻¹ , temp. 100° | | |
| 0 | 0.00834 | 100 |
| 15 | .00611 | 73 |
| 45 | .00376 | 45 |
| 150 | .00193 | 23 |
| Half-life 129 min., $k = 0.89 \times 10^{-4}$ sec. ⁻¹ , temp. 80° | | |
| 0 | 0.00838 | 100 |
| 30 | .00747 | 89 |
| 92 | .00485 | 58 |
| 180 | .00347 | 41 |

TABLE II

| Compound | Temp., °C. | $k \times 10^4$ |
|---|------------|-----------------|
| <i>p</i> -Deuteroanisole | 100 | 3.0; 3.0 |
| <i>p</i> -Deuteroanisole | 80 | 0.87; 0.89 |
| <i>o</i> -Deuteroanisole | 100 | 1.5 |
| <i>o</i> -Deuteroanisole | 80 | 0.29 |
| <i>p</i> -Deuterophenetole | 100 | 4.0 |
| <i>p</i> -Deutero- <i>n</i> -propyl ether | 100 | 4.0; 4.1 |
| <i>p</i> -Deutero-isopropyl ether | 100 | 7.2; 7.7 |

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