α-Oestradiol Dimethyl Ether, 17-Monomethyl Ether, and Related Compounds.

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Neither α-oestradiol dimethyl ether nor 17-monomethyl ether has been described. In order to fill up the vacancies in the literature the authors prepared these ethers and some related compounds. In view of the remarkably prolonged oestrogenic action of the dimethyl ether of diethylstilboestrol,⁽¹⁾ a similar physiological action of α-oestradiol dimethyl ether was expected.

α-Oestradiol dimethyl ether was prepared in a good yield by the action of dimethyl sulphate on the sodium compound from α-oestradiol 3-monomethyl ether and metallic sodium. The same substance was obtained in a smaller yield by the action of the methylating agent on the product from oestrone methyl ether and metallic sodium. The mechanism of the latter reaction is unknown. α-Oestradiol dimethyl ether forms colourless fine needles melting at 161–162° (corr.). It produced a prolonged oestrus in ovariectomized rats lasting 60 days by a single injection of 1 mg.

α-Oestradiol 3-monobenzoate failed to react with metallic sodium, and defied the attempt to methylate it through a sodium derivative. α-Oestradiol 17-monomethyl ether was prepared in a good yield by a partial demethylation of the dimethyl ether with hydroiodic acid and glacial acetic acid, while α-oestradiol was given by a more drastic demethylation. The 17-monomethyl ether forms colourless fine needles melting at 213.5–214.5° (corr.). It is insoluble in cold and even hot 5% aqueous caustic alkali

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(1) E. C. Dodds, L. Golberg, W. Lawson, and R. Robinson, *Proc. Roy. Soc.* (London), B, **127** (1939), 140.

in spite of the free phenolic hydroxyl group. It gives a 3-benzoate forming fine prisms melting at 165.5–166.5° (corr.), and a 3-*p*-toluene-sulphonate melting at 124.5–125.5° (corr.). In rat tests the 17-monomethyl ether showed a threshold value (less than 2.5 γ) approximating to that of oestrone (2 γ), and caused a duration of oestrus comparable to that caused by oestrone methyl ether.

Further the following derivatives of α-oestradiol were prepared: α-oestradiol 3-methyl ether 17-acetate, m.p. 103.5–104.5° (corr.); α-oestradiol 3-methyl ether 17-benzoate, m.p. 131–132° (corr.); α-oetradiol 3-methyl ether 17-*p*-toluene-sulphonate, m.p. 160–161° (corr.); α-oestradiol 3-benzoate 17-*p*-toluene-sulphonate, m.p. 184.5–185.5° (corr.); α-oestradiol 17-mono-*p*-toluene-sulphonate, m.p. 171–172° (corr.); and α-oestradiol di-*p*-toluene-sulphonate, difficultly crystallizable.

The new ethers of α-oestradiol were compared with some known substances in the physiological activity for ovariectomized rats.(2) Table 1 shows the minimum active doses obtained by single subcutaneous injections in oil solution. Table 2 records the duration of oestrus caused by single subcutaneous injections of 1 mg. and of 50 γ in oil solution.

Table 1. The Minimum Doses to Produce Oestrus in Ovariectomized Rats by Single Subcutaneous Injections.

Substance	Minimum active dose (γ)
α-Oestradiol	0.4
α-Oestradiol 3-monomethyl ether	4~5
α-Oestradiol 17-monomethyl ether	< 2.5
α-Oestradiol dimethyl ether	<10*
α-Oestradiol 17-mono-*p*-toluene-sulphonate	ca. 100
Oestrone	2
Oestrone methyl ether	15
Diethylstilboestrol	0.5
Diethylstilboestrol dimethyl ether	5

* No response with 5 γ.

Table 2. The Duration of Oestrus in Ovariectomized Rats Caused by Single Subcutaneous Injections.

Substance	Duration of Oestrus (Days)	
	1 mg.	50 γ
α-Oestradiol 3-monobenzoate		18
α-Oestradiol 3-monomethyl ether		5
α-Oestradiol 17-monomethyl ether	18	5~6
α-Oestradiol dimethyl ether	60	24
α-Oestradiol 17-mono-*p*-toluene-sulphonate	4~5	no response
Oestrone		6
Oestrone benzoate		10
Oestrone methyl ether	17	5
Diethylstilboestrol		3
Diethylstilboestrol dimethyl ether	26,52**	38

** Two animals died on the 26th day of oestrus and one on the 52nd day.

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Experimental.

α-Oestradiol Dimethyl Ether. A solution of α-oestradiol 3-monomethyl ether (m.p. 95–97°, corr.) in a small volume of pure ether was added to an excess of finely granulated metallic sodium. A white deposit separated out gradually with evolution of hydrogen gas. The mixture was left to stand overnight with exclusion of moisture. Dimethyl sulphate was added in a slight excess to sodium and the mixture was heated for an hour under a reflux condenser. To make sure that the reaction was complete, ether was distilled off and the residue was heated in benzene for an hour. The benzene solution was filtered from insoluble matters and evaporated. A light-yellow oil remained and solidified to a crystalline mass in a short time. It was repeatedly recrystallized from acetone. α-Oestradiol dimethyl ether thus obtained forms colourless fine needles melting at 161–162° (corr.). The yield of a pure substance about 60% of the 3-monomethyl ether. (Found: C, 80.3, 80.4; H, 9.4, 9.4. Calculated for $C_{20}H_{28}O_2$: C, 79.96; H, 9.39%.)

A large excess (400 mg.) of finely granulated metallic sodium was added to a solution of oestrone methyl ether (m.p. 168–169°, corr.) (1 g.) in anhydrous benzene (10 c.c.). No change was noticed to occur in the cold. When the mixture was boiled for five hours it became orange-red. On adding dimethyl sulphate (3 c.c.) an active reaction took place and the liquid became light-yellow. After boiled for an hour, the benzene solution was filtered, washed with water, 5% caustic soda, and again with water, dried, and evaporated. A reddish brown oil was obtained. When it was dissolved in a small amount of acetone and the resulting solution was left to stand for a day or two, a crystalline substance (100 mg.) separated out. It was collected and recrystallized twice from acetone. The substance thus obtained melted at 158–159° (corr.) and showed no depression of the melting point in admixture with a specimen (m.p. 159–160°) of oestradiol dimethyl ether obtained from oestradiol 3-monomethyl ether.

α-Oestradiol 17-Monomethyl Ether. A mixture of a glacial acetic acid solution of the dimethyl ether from oestradiol 3-monomethyl ether and hydroiodic acid (specific gravity 1.7)in a quantity equal to that of acetic acid was heated for 30 minutes on a boiling water bath, poured into water, and extracted with ether. The ethereal solution was washed successively with water, 5% aqueous soda, 5% sodium thiosulphate, and again with water, dried, and evaporated. The oily residue solidified to a crystalline mass. It was repeatedly recrystallized from methanol. Fine needles melting at 213.5–214.5° (corr.). Yield 60% of the dimethyl ether. The 17-monomethyl ether is insoluble in cold and hot 5% aqueous alkali.

The specimen of the dimethyl ether obtained from oestrone methyl ether could be demethylated to the same 17-monomethyl ether.

α-Oestradiol 17-Methyl Ether 3-Benzoate. The 17-monomethyl ether was dissolved in pyridine and benzoyl chloride was added. The mixture was left to stand for a week and poured into cold water. An oily precipitate separated out and crystallized immediately. Recrystallization from acetone gave fine prisms melting at 165.5–166.5° (corr.).

α-Oestradiol 17-Methyl Ether 3-*p*-Toluene-sulphonate. The 17-monomethyl ether was dissolved in pyridine and *p*-toluene-sulphonyl chloride was added. After standing for a day or two water was added and the mixture was well stirred to crystallization. The crystalline substance was collected and recrystallized from acetone. Melting point 124.5–125.5° (corr.).

α-Oestradiol 3-Methyl Ether 17-Acetate. Prepared from oestradiol 3-monomethyl ether and acetic anhydride in pyridine. Glittering scaly crystals melting at 103.5–104.5 (corr.).

α-Oestradiol 3-Methyl Ether 17-Benzoate. Oestradiol 3-monomethyl ether was dissolved in pure pyridine and benzoyl chloride was added with cooling. The mixture was left to stand at room temperature for a week and poured into ice water. An orange-coloured oil separated out and crystallized slowly. It could be crystallized completely by stirring with a small quantity of methanol. Recrystallization from acetone gave small prisms melting at 131–132° (corr.).

α-Oestradiol 3-Methyl Ether 17-*p*-Toluene-sulphonate. Prepared from oestradiol 3-monomethyl ether and *p*-toluene-sulphonyl chloride in pyridine. Melting point 160–161° (corr.).

α-Oestradiol 3-Benzoate 17-*p*-Toluene-sulphonate. Oestradiol 3-monobenzoate (m.p. 193–194°, corr.) was dissolved in pure pyridine and *p*-toluene-sulphonyl chloride was added. After standing for a day or two water was added to the mixture. The precipitate was recrystallized from acetone. Melting point 184.5–185.5° (corr.). Yield nearly theoretical.

α-Oestradiol 17-Mono-*p*-toluene-sulphonate. The above 3-benzoate 17-*p*-toluene-sulphonate was saponified partially with alcoholic potash, and the product was recrystallized from methanol. The substance melts at 171–172° (corr.) to a deep red liquid. It is difficultly soluble in 5% aqueous alkali. On acylation with *p*-toluene-sulphonyl chloride and pyridine it yielded the difficultly crystallizable di-*p*-toluene-sulphonate.

α-Oestradiol Di-*p*-toluene-sulphonate. Oestradiol was treated with *p*-toluene-sulphonyl chloride in pyridine. The product crystallized very slowly. On saponification by boiling with alcoholic potash it gave oestradiol 17-mono-*p*-toluene-sulphonate melting at 172–173° (corr.) alone and in admixture with the above specimen.

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