Some Mono- and Di-alkyl Ethers of Stilboestrol[1]

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For a study of the variation of the physical and pharmacological properties of the members of a series, the mono- and di-alkyl ethers of stilboestrol[2] (*trans*-4,4'-dihydroxy-α,β-diethylstilbene) seemed to be desirable. The parent compound has an intense physiological activity which can be determined readily and comparatively accurately. The dimethyl ether and several of the esters are known to have similar activity. The nonyl. The hexyl, octyl and decyl di-ethers have extremely low activity. The lower mono-ethers are 8 to 15 times as active as the corresponding di-alkylated compounds.[3] The figures given are the weights in gamma of the compounds which equal one rat unit as found by the Allan–Doisy method. The rat unit is the minimum amount of the estrogen required to produce cornification of the vaginal smear in 50% or more of a group of ten cas-

TABLE I

MELTING POINTS, ACTIVITIES AND ANALYSES OF THE MONO- AND DI-ALKYL ETHERS OF STILBOESTROL

The melting points were all taken on the same thermometer, calibrated for 3-inch immersion.

Alkyl	Melting points, °C. Mono-	Di-	Activity, γ Mono-	Di-	Analyses, mono- Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Analyses, di- Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found
Methyl	117[a]	124[b]	2.5[c]	20	...	...	...	...	...	...	...	...
Ethyl	99.5[d]	127.5[b]	5	50	81.08	80.62	8.11	8.10	81.48	81.10	8.64	8.82
Propyl	107	95.6[b]	17.5	250	81.29	80.97	8.39	8.27	81.81	81.66	9.09	9.44
Butyl	97.5	101.6	20	250	81.48	81.07	8.64	8.62	82.10	81.39	9.47	9.53
Amyl	82	64.6	48	600	81.65	81.69	8.87	8.81	82.35	82.17	9.81	9.91
Hexyl	72	74.6	45	30,000	81.81	81.05	9.09	9.04	82.56	82.38	10.09	10.13
Heptyl	87	50.4	45	750	81.96	81.84	9.29	9.38	82.75	82.58	10.34	10.37
Octyl	88.5	72.2	50	>50,000	82.10	81.80	9.47	9.75	82.92	82.97	10.56	10.54
Nonyl	76	57.4	50	5,000	82.23	81.88	9.64	9.63	83.07	83.05	10.76	11.01
Decyl	75	73.6	84	50,000	82.35	81.65	9.81	9.65	83.21	82.86	10.95	11.00
Undecyl	58.5	66.0	200	>40,000	82.46	81.68	9.95	9.89	83.33	82.71	11.11	11.01
Lauryl	83	80.0	100	.....	82.56	82.48	10.09	10.01	83.44	83.16	11.26	11.13
Tridecyl	67	73.2	...	.....	82.66	81.94	10.22	10.23	83.54	83.44	11.39	11.41
Myristyl	85	86.0	...	.....	82.75	82.81	10.34	10.68	83.63	83.67	11.51	11.94
Pentadecyl	73	77.0	...	.....	82.84	82.38	10.46	10.41	83.72	83.62	11.62	11.76
Cetyl	89	89.0	...	.....	82.92	81.93	10.56	10.27	83.80	83.64	11.73	12.06
Heptadecyl	78.5	82.0	...	.....	83.00	82.14	10.67	10.65	83.87	83.54	11.82	11.74
Octadecyl	94.3	94.0	...	.....	83.07	82.91	10.76	10.57	83.93	83.48	11.91	11.86

[a] The m. p. is 112–114° when it is recrystallized from aqueous alcohol and 116–117.5° from benzene–petroleum ether or from methylene chloride. *Anal.* Methoxyl calcd., 11.0; found, 10.9. [b] Sondern, Sealey and Kartsonis give 121–123°, 119–121° and 93–94° as the melting points of dimethyl, diethyl and dipropyl ethers, *Endocrinology*, **28**, 849 (1941). [c] Stilboestrol by same method 0.3 γ. [d] The mono-ethyl may have water of crystallization at times. One sample from aqueous alcohol, m. p. 105.5–107°, lost 6.0% on drying, calcd. for 1 water 5.7%, and then m. p. 99.5°.

mono-alkyl ethers appeared to be particularly interesting since, having one phenolic hydroxyl open, they might be expected to resemble the parent substance more closely than the dialkyl ethers.

We have prepared the mono- and di-ethers of stilboestrol using the normal alkyls from methyl to octadecyl. The melting points, activities and analyses are given in Table I and the melting points are plotted in Fig. 1.

In each series the estrogenic activity decreases as the alkyl increases in size, though in the mono-ethers there is not much change from amyl to

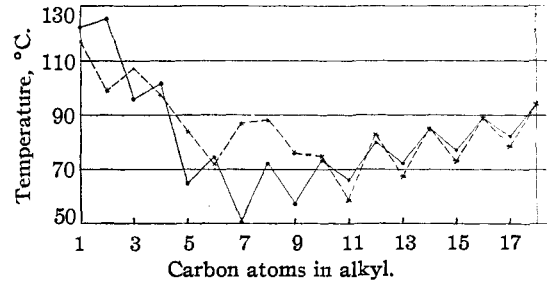

Fig. 1.—Melting points of the mono- and di-alkyl ethers of stilboestrol: —*—*—, mono-ethers; —●—●—, di-ethers.

(1) Read at the Atlantic City Meeting, September, 1941.

(2) E. C. Dodds, L. Goldberg, W. Lawson and R. Robinson, *Proc. Roy. Soc.* (London), **B127**, 152 (1939).

(3) Biological assays by C. F. Geschickter and Elizabeth W. Byrnes, published in part in *J. Clinical Endocrinology*, **2**, 19–25 (1942).

trated female rats. The melting points of the di-ethers show regular alternation; those of the mono- do so from the decyl up.

Experimental

These ethers were prepared in the conventional manner by heating stilboestrol in alcoholic solution with alkali and the required alkyl bromide (or iodide for the methyl). The preparation of the di-ethers presented no difficulty. These (particularly the high alkyl di-ethers) are much less soluble than the corresponding mono-ethers and can be purified by two or three recrystallizations from alcohol. To get rid of traces of mono-ether, alkali was usually added in the first recrystallization. The yields were high, usually above 90%. The mono-ethers proved to be difficult to prepare. The exclusive formation of a mono-ether could not be obtained by any attempted modification of the alkylation procedure. With less than one equivalent of alkyl halide and alkali the product always contained di-ether along with unreacted stilboestrol. Although stilboestrol is soluble in 0.1 *N* aqueous alkali and the mono-ethers only in alcoholic alkali, the separation, theoretically simple, is tedious in practice. Since the solubilities change greatly with the size of the alkyl, each mono-ether required special study. In some cases the separation was repeated as many as 10 times before a satisfactory product was obtained. For the monomethyl ether 0.4 *N* potassium hydroxide in 50% alcohol was used; the higher mono-ethers required stronger alcohol.

The monomethyl ether was recrystallized from 70% ethanol and then distilled *in vacuo*, b. p. 185–195° (0.3 mm.).

Summary

1. The normal mono- and di-alkyl ethers of stilboestrol from methyl to octadecyl have been prepared.

2. Their estrogenic activities have been determined.

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The Effect of Temperature on the Validity of Hudson's Rules of Isorotation

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Over thirty years ago, Hudson[1] proposed his "rules of isorotation" for use in calculating the optical rotatory powers of carbohydrate derivatives. Although these have since been of great use to the carbohydrate chemist in determining the structure of new derivatives, their reliability has been seriously reduced by the existence of a number of definite instances, notably but not solely in the mannose series, in which calculated rotations fail to agree at all satisfactorily with those observed. It has been felt that if the source of these discrepancies could be determined, the value of the rules as a tool in carbohydrate structure determination might be considerably enhanced. So far, the effects of different solvents and concentrations[2] and of wave length[3] on carbohydrate rotations have been studied, but the behavior of the anomalous cases with respect to these variables has not led to any clue as to the true nature of the difficulty. Previous theoretical considerations,[4] based upon the physical origin of optical rotation have led us to suspect that the real clue to the problem is to be found in temperature dependence of the rotation. In this paper we shall give the reasoning which leads to this conclusion and show by means of experimental data that there is indeed good reason to believe that this is actually the case.

In a previous paper[4] it was shown by relatively simple, essentially geometrical arguments that Hudson's rules may be expected to be valid if two conditions are fulfilled. (1) The vicinal actions between any two groups whose locations, conformations and relative orientations in a molecule are fixed must be unaffected by change in the spacial configurations of other groups in the molecule.[5] In order to state this more explicitly,

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(1) C. S. Hudson, THIS JOURNAL, **31**, 66 (1909).

(2) P. Levene and I. Bencowitz, *J. Biol. Chem.*, **73**, 685 (1927).

(3) T. L. Harris, E. L. Hirst and C. E. Wood, *J. Chem. Soc.*, 2108 (1932).

(4) E. Gorin, W. Kauzmann and J. Walter, *J. Chem. Phys.*, **7**, 327 (1939).

(5) Vicinal actions are the optical interactious between groups in a molecule, the sum total of which results in the molecule's being able to rotate the plane of polarized light. For further details, see W. Kauzmann, J. Walter and H. Eyring, *Chem. Rev.*, **26**, 339 (1940).