closely to that of 2,4-dipyridyl, but was not further identified.

DEPARTMENT OF CHEMISTRY
STANFORD UNIVERSITY
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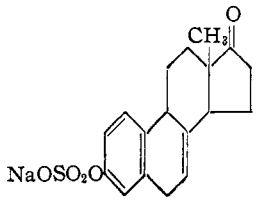
Sodium Equilin Sulfate and Sodium Equilenin Sulfate

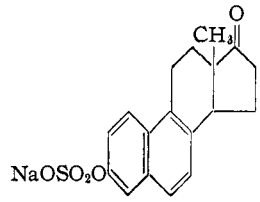
BY GORDON A. GRANT AND WILLIAM L. GLEN

We wish to report the synthesis and biological activity of two new estrogen sulfates, namely, sodium equilin sulfate, and sodium equilenin sulfate.

The method employed was that previously reported by Butenandt and Hofstetter[1] for the preparation of sodium estrone sulfate.



I



II

Sodium Equilin Sulfate (I).—Equilin (1.13 g.) dissolved in a mixture of dry pyridine (19.8 ml.) and dry chloroform (39.6 ml.) was added with cooling to 0.32 ml. chlorosulfonic acid in dry chloroform (19.8 ml.) plus dry pyridine (9.9 ml.). After twenty four hours at room temperature, the solvents were removed from the reaction mixture by concentration *in vacuo* at 27°. The residue, after washing with dry ether, was dissolved in methanol, and neutralized with *N* methanolic sodium hydroxide, to *p*H 7.8. Inorganic salt was removed by centrifugation, and the sodium equilin sulfate (1.10 g.) was obtained from the methanol solution, by fractional precipitation with ether, as a white solid soluble in water. It contained 76% equilin as determined colorimetrically by a modified Marrian–Kober test[2] (required 72.4), and had $[\alpha]^{20}D$ + 218° (H_2O). *Anal.* Calcd. for $C_{18}H_{19}O_5SNa$: C, 58.37; H, 5.13; S, 8.64. Found: C, 58.20; H, 5.10; S, 8.40.

The quinidine salt was prepared by precipitation from an aqueous solution of the sodium salt. *Anal.* Calcd. $C_{38}H_{44}O_7N_2S$: N, 4.16; equilin, 39.9. Found: N, 4.03; equilin, 45.

Sodium Equilenin Sulfate (II).—Sodium equilenin sulfate (260 mg.), from 570 mg. of equilenin, was isolated as described above, except that the final methanol solution required decolorizing with a little norite.

It was a white solid soluble in water, and contained 70% equilenin (required 68.9%), and had an $[\alpha]^{20}D$ + 70° (H_2O). *Anal.* Calcd. $C_{18}H_{17}O_5SNa \cdot H_2O$: C, 55.95; H, 4.92; S, 8.29. Found: C, 55.59; H, 4.86; S, 8.31.

The quinidine salt prepared as above contained 42% equilenin ($C_{38}H_{42}O_7N_2S$ requires 39.7).

Biological Activity.—The compounds were assayed for their estrogenic activity by oral administration to adult ovariectomised rats. The amount (total dose) of each compound which brought about a 50% estrogenic response (RD 50) is given below. Results obtained with sodium estrone sulfate[3] are included for comparison. The values in parentheses are those obtained for the unesterified estrogens in each case, *i. e.*, estrone, equilin and equilenin.

Compound	RD 50 (Total dose) γ
Sodium estrone sulfate	148 (249)
Sodium equilin sulfate	108 (210) 120
Sodium equilenin sulfate	1200 (1000)

Sodium estrone sulfate and sodium equilin sulfate were each considerably more active than the respective unconjugated estrogen, when assayed in the above manner. The sodium equilenin sulfate was a much less active estrogen.

RESEARCH AND BIOLOGICAL LABS.
AYERST, MCKENNA AND HARRISON, LTD.
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(1) Butenandt and Hofstetter, *Z. physiol. Chem.*, **259**, 222 (1939).

(2) Venning, Evelyn, Harkness and Browne, *J. Biol. Chem.*, **120**, 225 (1937).

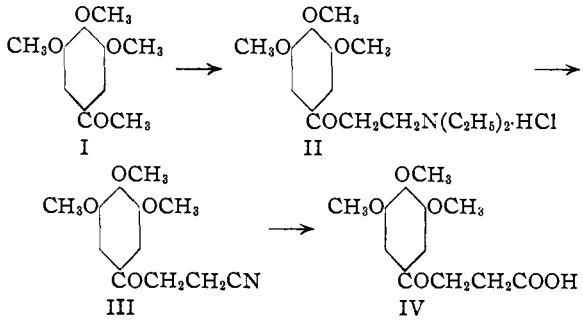
(3) Grant and Souch, Biological Division, Pittsburgh meeting of the American Chemical Society, September, 1948.

The Preparation of β-(3,4,5-Trimethoxybenzoyl)-propionic Acid

BY ELEANOR HAGGETT AND S. ARCHER

In connection with some other work the need arose for substantial quantities of β-(3,4,5-trimethoxybenzoyl)-propionic acid. This substance had been prepared previously by Haworth and co-workers[1] who alkylated ethyl 3,4,5-trimethoxybenzoylacetate with ethyl bromoacetate and then hydrolyzed and decarboxylated the resulting diester.

Since, in our hands, the method did not seem to be entirely satisfactory we resorted to the preparation outlined in the following equations.



The required ketone, I, was prepared from 3,4,5-trimethoxybenzoyl chloride according to Hauser's method.[2] The ketone was converted to II under the usual Mannich conditions. In addition, the corresponding piperidyl and dimethylamino ketones were prepared. The salt, II, gave better yields of the nitrile, III, than either the piperidyl or dimethylamino derivatives, when treated with potassium cyanide in dilute hydrochloric acid solution.[3] Preliminary experiments indicated that the conversion of the nitrile to the acid, IV, proceeded in better yield when carried out stepwise through the intermediate ethyl ester rather than by direct acid hydrolysis. In this way the desired acid, IV, was obtained in 21% over-all yield from 3,4,5-trimethoxybenzoyl chloride.

(1) Haworth, Richardson and Sheldrick, *J. Chem. Soc.*, **135**, 1580 (1935).

(2) Walker and Hauser, THIS JOURNAL, **68**, 1386 (1946).

(3) Knott, *J. Chem. Soc.*, 1190 (1947).