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

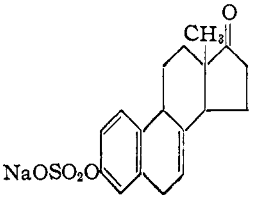
Department of Chemistry
Stanford University
Stanford, California
Received February 25, 1949

Sodium Equilin Sulfate and Sodium Equilenin Sulfate

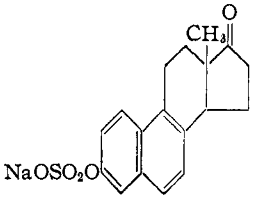
By Gordon A. Grant and William L. Glen

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 $[\alpha]^{20}\mathrm{D}$ + 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 $[\alpha]^{20}\mathrm{D}$ + 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.
Montreal, Canada
Received March 21, 1949

---

[1] Butenandt and Hofstetter, *Z. physiol. Chem.*, **259**, 222 (1939).

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

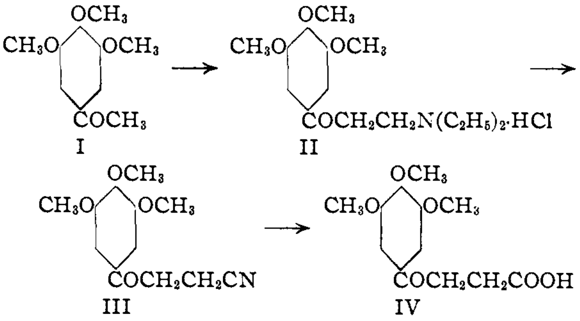
[3] Grant and Souch, Biological Division, Pittsburgh meeting of the American Chemical Society, September, 1943.

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).

Experimental[4]

3,4,5-Trimethoxyacetophenone.—In accordance with the directions of Hauser[2] we obtained 29.8 g. of the ketone, m. p. 72–74°, from 46.0 g. of the corresponding acid chloride (yield, 71%). After further recrystallization from benzene–ligroin the melting point was raised to 79–81°.

β-Piperidyl-3,4,5-trimethoxypropiophenone Hydrochloride.—A mixture of 26.3 g. of the above ketone, 15.3 g. of piperidine hydrochloride, 5.6 g. of paraformaldehyde and 37.5 ml. of absolute ethanol containing 0.25 ml. of concentrated hydrochloric acid was heated under reflux for one hour. Then 3.8 g. of paraformaldehyde was added and heating continued for an additional two hours. The hot mixture was treated with 300 ml. of acetone, refluxed for fifteen minutes, cooled and filtered. There was obtained 30.3 g. (71%) of the desired salt. The analytical sample, which was crystallized twice from absolute ethanol–ether, melted at 194.4–195.2° (cor.).

Anal. Calcd. for $C_{17}H_{25}NO_4 \cdot HCl$: C, 59.38; H, 7.62; N, 4.07. Found: C, 59.29; H, 7.42; N, 3.98.

β-Dimethylamino-3,4,5-trimethoxypropiophenone Hydrochloride.—When an equivalent quantity of dimethylamine hydrochloride was substituted for the piperidine hydrochloride in the above experiment, the corresponding salt was obtained in 71% yield. Two recrystallizations from dry ethanol–ether gave the pure product, m. p. 174.5–175.3° (cor.).

Anal. Calcd. for $C_{14}H_{21}O_4N \cdot HCl$: C, 55.34; H, 7.30; N, 4.61. Found: C, 55.31; H, 7.25; N, 4.74.

β-Diethyl-3,4,5-trimethoxypropiophenone Hydrochloride.—This salt was obtained in 66% yield when diethylamine hydrochloride was used in the above procedure. The pure compound was obtained after two crystallizations from alcohol–ether; m. p. 144.8–146.5° (cor.).

Anal. Calcd. for $C_{16}H_{25}O_4N \cdot HCl$: C, 57.91; H, 7.90; Cl, 10.68. Found: C, 58.00; H, 8.02; Cl, 10.66.

β-(3,4,5-Trimethoxybenzoyl)-propionitrile.[3]—A solution of 60.6 g. of β-diethylamino-3,4,5-trimethoxypropiophenone hydrochloride, 15.2 ml. of concentrated hydrochloric acid and 1900 ml. of water was heated and stirred under reflux while 47.6 g. of potassium cyanide dissolved in 180 ml. of water was added beneath the surface of the liquid over a twenty-minute period. After one hour the mixture was cooled and the solid collected. The product from two such runs was crystallized from dilute ethanol to give the nitrile, m. p. 115–116.5°; yield, 65%. A small sample was crystallized from ethanol and analyzed; m. p. 115.5–116.5°.

Anal. Calcd. for $C_{13}H_{15}NO_4$: C, 62.64; H, 6.07. Found: C, 62.99; H, 6.08.

β-(3,4,5-Trimethoxybenzoyl)-propionic Acid.—A mixture of 12.5 g. of the nitrile, 12.0 ml. of ethanol and 5.5 ml. of sulfuric acid was refluxed for sixteen hours and poured onto ice-water. The mixture was made slightly basic and the solid ester collected. It was refluxed for four hours with 10% sodium hydroxide. The mixture was diluted with an equal volume of water, acidified with hydrochloric acid and cooled. After several hours in the ice-chest, the acid was collected on a filter and dried; wt. 9.9 g. (66%). After crystallization from benzene the product melted at 120–121°. (Haworth[1] reported 121–122° as the melting point for the acid.)

---

[4] The analyses were carried out under the supervision of Mr. M. E. Auerbach.

STERLING-WINTHROP RESEARCH INSTITUTE
RENSSELAER, NEW YORK
RECEIVED FEBRUARY 16, 1949

Interaction of Ferric Ions with Silicic Acid

BY FRED HAZEL, RICHARD U. SCHOCK, JR., AND MAXWELL GORDON

Application of synthetic base exchange resins to the preparation of colloidal silicic acid[1] provides a method for obtaining this system in a pure form without resorting to prolonged dialysis. The saving in time affords a particular advantage in the case of silicic acid sols because the superposed aging with condensation to larger particles is avoided. It is clear that the use of freshly prepared systems gives a favorable opportunity for studying the reactions of the acid.[2]

Silicic acid sols containing 2.5 ± 0.1% silica were prepared by adding measured volumes of diluted sodium silicate to weighed portions of ion exchange resins in the hydrogen form as described previously.[2] The silicate had a sodium oxide–silica ratio by weight of 1:3.2 and was a standard commercial product ("E brand") of the Philadelphia Quartz Company.

Freshly prepared solutions of various salts were titrated with the freshly prepared acids. Changes in hydrogen ion concentration were followed with Leeds and Northrup *p*H meters employing glass electrodes. Preliminary experiments were carried out with barium chloride, lanthanum chloride, copper sulfate, chromic chloride, aluminum sulfate, aluminum chloride and ferric chloride. The first three salts gave no indication of interaction while that with chromic chloride was slight. Aluminum chloride and ferric chloride showed the greatest interaction.

Results obtained on mixing two volumes of silicic acid sol and one volume of various salt solutions are given in Table I.

TABLE I

INTERACTION OF COLLOIDAL SILICIC ACID WITH METALLIC IONS

*p*H silicic acid	Salt, *M*		Original *p*H	Final *p*H	Change in hydrogen ion concentration, *M*
2.21	0.1	$FeCl_3 \cdot 6H_2O$	1.77	1.70	0.003
2.21	.05	$FeCl_3 \cdot 6H_2O$	1.97	1.83	.004
2.21	.025	$FeCl_3 \cdot 6H_2O$	2.12	1.95	.0036
2.97	.2	$AlCl_3 \cdot 6H_2O$	3.07	2.52	.0021
3.20	.02	$AlCl_3 \cdot 6H_2O$	3.46	2.71	.0016
3.27	.1	$Al_2(SO_4)_3 \cdot 18H_2O$	3.02	2.87	.00044
3.27	.01	$Al_2(SO_4)_3 \cdot 18H_2O$	3.42	2.95	.00072
3.23	.02	$CrCl_3 \cdot 6H_2O$	3.30	3.17	.00018

The interaction with ferric chloride was manifest not only by the considerable increase in hydrogen ion concentration but also by the discharge of the color of the solution of ferric salt. Control experiments were carried out substituting various strong mineral acids for silicic acid, and these showed clearly that the reaction was due to silicic acid.

Additional experiments were conducted with a silicic acid sol prepared by mixing hydrochloric acid and sodium silicate.[3] This system also had a concentration of 2.5% silica and a *p*H of 2.2. The freshly prepared acid was used to titrate ferric chloride solutions of different concentrations. Titrations were repeated after the silicic

---

[1] Bird, U. S. Patent 2,244,325, June 3, 1941.

[2] Hazel, *J. Phys. Colloid Chem.*, 51, 415 (1947).

[3] Graham, *Pogg. Ann.*, 114, 187 (1861),