Experimental

Silver trifluoroacetate can be prepared by adding trifluoroacetic acid to a slight excess of suspended silver hydroxide, filtering, evaporating to dryness, grinding to a powder, and completing the desiccation *in vacuo*, on a steam-bath. The pure, dry salt is not sensitive to light.

From commercial sodium trifluoroacetate, an alternate method consists in dissolving silver nitrate in an equal amount of water, adding an equimolecular quantity of sodium trifluoroacetate, and extracting with portions of ether of about equal volume. Vigorous agitation for thirty minutes on a mechanical shaker is recommended, as the difference in density tends to keep the layers apart. After three extractions, it is well to distil off as much water as can be taken from the aqueous layer without causing crystallizing out, because the crystals are a mixture of sodium nitrate and silver trifluoroacetate. The extraction is then repeated with three portions of ether. On distillation, the ether solution leaves a mushy residue of silver salt and ether, which must be desiccated *in vacuo* on the steam-bath, as above.

Dry salt (0.3 mole) was finely ground and mixed with powdered iodine (0.32 mole). The mixture was placed in a horizontally held tube, 25 mm. in diameter and 25 cm. long; this tube was sealed at the far end, while its near end was connected to a wide trap cooled in ice water, backed by two traps cooled in Dry-Ice and a small water bubbler showing the rate of evolution of the carbon dioxide. The ice trap collected a fine sublimate of iodine and prevented clogging of the Dry-Ice traps, the first of which collected practically all of the trifluoroiodomethane.

The mixture of silver salt and iodine was heated cautiously with a gas burner, starting at the far end of the tube. The heat-decomposition is smooth at about 100°, but tends to propagate spontaneously and escape control when the heating is not done patiently. The bubbling of carbon dioxide is used as an indicator for the speed at which the burner can be moved toward the near end. With the small equipment used, it took 90 minutes to complete the reaction. The crude CF_3I amounted to 47 g., or 0.24 mole, an 80% yield. A series of larger runs averaged 87% yields. Purification was done by fractional distillation, which removed less than one gram of heads and tails and gave a material boiling at −21.8°, close to the reported[2] boiling point of −22.5°.

CF_3I is conveniently stored in glass ampules. Exposed to light it slowly becomes pink, then purple, which is in agreement with its reported easy dissociation into free radicals.

CONTRIBUTION NO. 1424 FROM THE
GATES AND CRELLIN LABORATORIES OF CHEMISTRY
CALIFORNIA INSTITUTE OF TECHNOLOGY
PASADENA, CALIFORNIA RECEIVED APRIL 28, 1950

Sodium Estradiol-3-benzoate-17-sulfate and Sodium Estradiol-17-monosulfate

BY GEORGE W. HOLDEN AND ROBERT BROMLEY

In a previous note the preparation of sodium testosterone sulfate was described.[1] Tests indicate that this compound is inactive androgenically in rats in ten times the effective dose of testosterone propionate, by subcutaneous injection in propylene glycol.

It therefore seemed of interest to prepare sodium estradiol-3-benzoate-17-sulfate and sodium estradiol-17-monosulfate, neither of which has been described previously, in order to compare their estrogenic activity with that of the corresponding free 17-hydroxyl compound. The results of the biological tests will be reported later.

Estradiol-3-mono-benzoate (I) was used as starting material for the preparation of sodium estradiol-17-monosulfate (III) which was readily obtained by saponification of the intermediate sodium estradiol-3-benzoate-17-sulfate (II).

(II) is insoluble in water but readily soluble in alcohol and propylene glycol. The ultraviolet absorption curve in alcohol is similar to that of (I). Neither (II) nor (I) exhibits a region of maximum absorption.

Sodium estradiol-17-monosulfate is soluble to the extent of approximately 0.5% in water at room temperature. At a concentration of 2% in water a thick gel is formed. It is readily soluble in alcohol and propylene glycol. In alcohol the characteristic absorption maximum for estradiol at 280 mμ was obtained; in water it was slightly displaced at 276–278 mμ.

Experimental

Sodium Estradiol-3-benzoate-17-sulfate.—A solution of chlorosulfonic acid, prepared by dissolving chlorosulfonic acid (2.4 ml.) in dry chloroform (72 ml.), cooling to 0° and adding dry pyridine (36 ml.), was added to a solution of estradiol-3-monobenzoate (5 g.) in dry pyridine (48 ml.) and dry chloroform (120 ml.). After sixty-eight hours at room temperature the solvent was removed *in vacuo* at a bath temperature of 40–50°. The residue was dissolved in methanol (125 ml.), the solution filtered from a small amount of insoluble matter and a 10% aqueous solution of sodium carbonate (55 ml.) was added to the clear filtrate. During this addition the product separated as a lustrous crystalline solid. The mixture was now poured into one liter of water and, after standing several hours, the solid was collected and washed with water (500 ml.). The product was dried *in vacuo* over sulfuric acid.

As thus obtained sodium estradiol-3-benzoate-17-sulfate starts to soften[2] at 155°, partially liquefies around 165° and yields a slightly opaque almost colorless fluid at 195° with effervescence; $[\alpha]^{25}D$ + 34.8° (1% in alc.). On heating to 110° in an oven it decomposes to yield estradiol benzoate.

Anal. Calcd. for $C_{25}H_{28}O_6SNa \cdot 0.5H_2O$: C, 61.5; H, 5.98; Na, 4.71. Found: C, 61.6; H, 5.8; Na, 4.6; yield, 6.49 g.; 100%.

Sodium Estradiol-17-monosulfate.—(II) (3 g.) was saponified by refluxing 1 hour in a solution of methanol (200 ml.) and sodium hydroxide (300 mg.). Water (100 ml.) was added to the cooled solution which was then treated with an excess of carbon dioxide. On removal of the bulk of methanol *in vacuo* at a bath temperature of 40–50°, the product separated. After short refrigeration it was collected, sucked as dry as possible and dried *in vacuo* over sulfuric acid. As thus obtained sodium estradiol-17-monosulfate shows no definite melting point but starts to decompose with formation of a brilliant red color at 160° and finally becomes liquid at 180° with effervescence and with color changing to orange yellow; $[\alpha]^{25}D$ + 42.5 (1% in alc.); + 15.8° (0.5% in water); ϵ (280) = 2000[3] (in alc.); ϵ (276–278) = 1770 (in H_2O). *Anal.* Calcd. for $C_{18}H_{24}O_5SNa \cdot H_2O$: C, 54.95; H, 6.66; Na, 5.85. Found: C, 54.79; H, 6.53; Na, 5.85; yield, 1.97 g.; 83.3%.

Hydrolysis of Sodium Estradiol-17-Monosulfate.—(a) Fifty milligrams was refluxed four hours with the barium chloride–sodium acetate mixture described by Talbot.[4] The solids which separated on cooling were filtered off and dried *in vacuo* over sulfuric acid. Forty-five milligrams (90%) was recovered, m. p. 135–150° with the red

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(1) Holden and Bromley, THIS JOURNAL, **71**, 3844 (1949).

(2) All melting points on Fisher–Johns apparatus.

(3) Estradiol in alc. gave an ϵ value at 280 mμ of 1985.

(4) Talbot, Ryan and Wolfe, *J. Biol. Chem.*, **148**, 598 (1943).

color characteristic of the starting material. The specific rotation was also unchanged from that of the starting material. (b) Fifty milligrams was refluxed with an aqueous hydrochloric acid–toluene mixture for one hour. Thirty milligrams (82%) of crude residue was obtained and recrystallized from aqueous ethanol to yield 20 mg. (55%) of estradiol, m. p. 167–170°.

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RECEIVED JANUARY 27, 1950

Electron Exchange between Manganate and Permanganate Ions by Solvent Extraction[1]

BY HOWARD C. HORNIG, GEORGE L. ZIMMERMAN AND W. F. LIBBY

The electron exchange reaction between manganate and permanganate ions in basic solution was reëxamined by using pyridine extraction to separate the permanganate from the reaction solution. With 4 *M* potassium hydroxide solutions pyridine has a fairly low solubility and it is observed that an essentially quantitative removal of MnO_4^- into the pyridine layer occurs while MnO_4^{--} is extracted to a negligible extent. The exchange was followed with the radioactive tracer Mn^{56} with 2.5 hour half life. The manganate–permanganate exchange was previously reported to be rapid when separation was made by precipitation of barium manganate,[2] but in view of the possibility of catalysis by precipitation, *viz.*, Prestwood and Wahl's study of thallous–thallic exchange[3] the solvent extraction method was tried. The exchange was again found too rapid to measure; even at 0° exchange was complete in thirty-five seconds.

TABLE I

Data on Exchange between MnO_4^{--} and MnO_4^- (both at 0.013 *M*)

Run	Temp., °C.	Contact time, sec.	Exchange, %	Active specie	Loss MnO_4^-, (%)	Material balance, %	Remarks
6	0	50	102 ± 3	MnO_4^{--}	1.2	4.4	Low activity
7	0	50	98.5 ± 3	MnO_4^{--}	8.2 gain	0.9 gain	Low activity
11	− 3	45	97.8 ± 2	MnO_4^{--}	1.4	2.3 loss	
12	− 3	45	99.1 ± 2	MnO_4^{--}	5.4	1.1 loss	
13	0	45	101.8 ± 2	MnO_4^{--}	24	12.5 loss	Very poor material balance
14	− 3	43	100	MnO_4^-	2.9	1	Good activity balance
15	− 3	42	100	MnO_4^-	0.6	1.6	Good activity balance
17	− 3	40	99.5 ± 2	MnO_4^-	2.1 gain	0.2 loss	$(MnO_4^-)/(MnO_4^{--}) = 0.37$
22	− 3	38	100	MnO_4^-			
25	− 4	40	99.4	MnO_4^-	0.5 gain	2.6 loss	
26	− 4	35	99.5	MnO_4^-	1 gain	1.7 loss	
27	−14	42	93.9 ± 2	MnO_4^-	7.8 gain	1.6 loss	Probably MnO_2 in system
28	−14	35	93.4 ± 2	MnO_4^-	6.8	3.6 loss	

Experimental

The manganate–permanganate exchange in 3.5 and 4 *M* aqueous potassium hydroxide solution was performed at 0° in order to retard the decomposition of permanganate in basic solution and to afford the best chance of finding a measurable rate of exchange. The loss of permanganate by reduction was between 2 and 5%, and material balance was found within 2 or 3%.

In a typical run 7.35 ml. of 0.0893 *M* K_2MnO_4 in 4 *M* KOH was added to 35 ml. of 4 *M* KOH in a separatory funnel; 7.0 ml. of 0.0939 *M* $KMnO_4$ containing radioactive Mn^{56} was delivered rapidly with a hypodermic syringe and mixed to give an equimolar solution of 0.013 *M*; 40 ml. of pyridine saturated with KOH was immediately added, shaken, and the layers separated. The probable time of contact was measured from the addition of permanganate until the two layers separated with a sharp interface; the total time was measured to the complete separation of the two phases. The pyridine, potassium manganate, and potassium hydroxide solutions were precooled to −3 or −4° in an ice-salt-water-bath, the potassium permanganate was cooled to 0°, and the entire experiment was performed in a refrigerated room at 7°. After the separation, the solutions were analyzed by precipitating $MnNH_4PO_4$, weighing as the monohydrate, and counting the activity of this precipitate.

It was found that the presence of large amounts of pyridine strongly interfered with the precipitation of $MnNH_4PO_4$, and its presence in small amounts discolored the precipitate. The pyridine which was dissolved in the aqueous phase was removed sufficiently well by heating to a slow boil for ten to fifteen minutes. To the pyridine phase was added 40 ml. of water and 5–10 ml. of 4 *M* KOH solution and stirred to form a pyridine–water solution saturated with KOH (a small amount of a second heavy phase separated). The permanganate was reduced to MnO_2 with 5% hydrogen peroxide. Then 10–15 pellets of KOH were added and, after vigorous stirring, a deep aqueous layer separated into which all of the MnO_2 settled. The pyridine was drawn off the top with a pipet and discarded, and the aqueous layer boiled ten to fifteen minutes to remove the remaining pyridine.

Both solutions were then acidified with hydrochloric acid and the manganese reduced to Mn^{++} with 5% hydrogen peroxide. According to the procedure described by Hillebrand and Lundell,[4] the volume of the solution was adjusted to about 130 ml., 15 g. ammonium chloride and 1.5 g. dibasic ammonium phosphate were added. The $MnNH_4PO_4$ was precipitated from the boiling solutions by adding dropwise dilute ammonium hydroxide. The cooled solutions were filtered and washed with water onto a previously washed and weighed filter paper and dried for forty minutes at 75–80° to the monohydrate,[5] weighed, mounted, and counted using an Eck and Krebs thin-wall counter tube.

The University of Chicago cyclotron or a radium–

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(1) This work was assisted by the Office of Naval Research under Task Order III of Contract N6ori-20.

(2) W. F. Libby, THIS JOURNAL, **62**, 1930 (1940).

(3) R. J. Prestwood and A. C. Wahl, *ibid.*, **71**, 3137 (1949).

(4) W. F. Hillebrand and G. E. F. Lundell, "Applied Inorganic Analysis," John Wiley and Son, New York, N. Y., 1929.

(5) J. W. Mellor, "Treatise on Inorganic and Theoretical Chemistry," **12**, 452, Longmans, Green, New York, N. Y., 1932.