EUROPEAN PHARMACOPOEIA

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VOLUME I

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METHODS OF ANALYSIS

CHEMICAL METHODS

ASSAYS

DETERMINATION BY THE OXYGEN COMBUSTION METHOD

Page 112. **Sulphur 1.** Replace in the 8th line " 500 ml " by " 50 ml ".

SEMI-MICRO DETERMINATION OF WATER

Pages 117 and 118. Replace the text by the following:

" The titration vessel, of about 60 ml capacity, is fitted with two platinum electrodes, a nitrogen inlet tube, a stopper which accommodates the burette tip, and a vent tube protected by a desiccant. The substance to be examined is introduced through an inlet tube or side arm which can be closed by a ground stopper. Stirring is effected magnetically or by means of a stream of dried nitrogen passed through the solution during the titration.

The end-point may be determined electrometrically using a 1·5 volt battery and a variable resistance of about 2 000 ohms. The resistance is adjusted so that an initial current passes through platinum electrodes connected in series to an ammeter. On adding the reagent the needle of the ammeter shows a deflection but returns immediately to its starting position. At the end of the reaction a deflection is obtained which persists for not less than half a minute.

Use the iodosulphurous reagent R after determination of the water equivalent (Vol. I, page 165). The reagents and solutions used in this method must be kept anhydrous and precautions must be taken throughout to prevent exposure to atmospheric moisture. The iodosulphurous reagent R is protected from light, preferably stored in a bottle to which is fitted an automatic burette.

Unless otherwise prescribed, the determination of water is carried out by Method A.

Method A.

Add about 20 ml of anhydrous methanol R to the titration vessel and titrate to the electrometric end-point with the iodosulphurous reagent R. Transfer quickly the prescribed amount of the substance to be examined, accurately weighed, to the titration vessel. Stir for 1 minute, and titrate again to the electrometric end-point using iodosulphurous reagent R.

Method B.

Add about 10 ml of anhydrous methanol R to the titration vessel and titrate to the electrometric end-point with iodosulphurous reagent R. Transfer quickly the prescribed amount, accurately weighed, of the substance to be examined in a suitable state of division followed by an accurately measured amount of iodosulphurous reagent R, sufficient to give an excess of about 1 ml. Allow to stand protected from light for 1 minute or the time prescribed in the monograph, stirring from to time.

Titrate the excess of iodosulphurous reagent R to the electrometric end-point with anhydrous methanol R to which has been added an accurately known amount of water, equivalent to about 0·25 per cent w/v. "

REAGENTS

Page 132. **Ammonia, concentrated**

Replace the text of solution S by the following:

" Evaporate 220 ml on a water bath almost to dryness, cool, add 1 ml of dilute acetic acid R and dilute to 20 ml with water. "

Page 155. Insert after the reagent " Emetine dihydrochloride ":

" **Ergosterol** — $C_{28}H_{44}O,xH_2O$.

Contains not less than 98·0 per cent and not more than the equivalent of 102·0 per cent of $C_{28}H_{44}O$, calculated with reference to the anhydrous substance.

White or almost white needles or a crystalline powder, practically insoluble in water, soluble in chloroform, sparingly soluble in ether, slightly soluble in ethanol.

mp: about 163°, with decomposition (instantaneous method).

A 0·001 per cent w/v solution in ethanol R shows absorption maxima at about 260, 271, 282 and 294 nm.

$[\alpha]_D^{20}$: −131° to −136°, determined on a 2·0 per cent w/v solution in chloroform R and calculated with reference to the anhydrous substance.

Water (Suppl. Vol. II, page 7). Not more than 6·5 per cent w/w, determined on 0·500 g.

Assay. Dissolve about 15·0 mg, accurately weighed, in ethanol R and dilute to 100·0 ml with the same solvent. Dilute 5·0 ml of the solution to 50·0 ml with the same solvent. Measure the extinction (Vol. I, page 83) at the absorption maximum at about 282 nm in a 1 cm cell.

Calculate the content of $C_{28}H_{44}O$ taking the specific extinction $E\,\frac{1\text{ per cent}}{1\text{ cm}}$ to be 306.

Store in a well-closed container, protected from light and air. "

Page 163. Insert after the reagent " Hydrogen sulphide ":

" **Hydroquinone** — $C_6H_6O_2$ (MW 110·1).

Contains not less than 99·0 per cent of $C_6H_6O_2$.

Fine, colourless or white needles, darkening on exposure to air and light soluble in water, in alcohol and in ether.

mp: 172° to 174°.

Assay. Dissolve about 0·250 g, accurately weighed, in a mixture of 100 ml of water and 10 ml of 0·1N sulphuric acid. Add 1 ml of diphenylamine solution R and titrate with 0·1N ammonium and cerium nitrate until a red-violet colour is obtained.

1 ml of 0·1N ammonium and cerium nitrate is equivalent to 5·506 mg of $C_6H_6O_2$.

Store in a well-closed container, protected from light and air. "

Page 167. **Lead subacetate solution**

Replace in the first and second lines:

" w/v " by " w/w ".

Page 184. **Potassium hydroxide**

Replace the first sentence of the test for heavy metals by the following:

" Dissolve 1·5 g in 10 ml of water, neutralise with 3 ml of hydrochloric acid R and dilute to 15 ml with water. "

Page 191. **Sodium acetate** — $C_2H_3NaO_2$, $3H_2O$ (MW 136·1).

Replace the text by the following:

" Contains not less than 99·5 per cent of $C_2H_3NaO_2,3H_2O$.

Colourless crystals, very soluble in water, soluble in alcohol.

Solution S. Dissolve 10·0 g in water and dilute to 100 ml with the same solvent.

Appearance of solution. Solution S is clear (Method B, Vol. I, page 57) and colourless (Method II, Vol. I, page 59).

pH (Vol. I, page 63). The pH of a mixture of equal volumes of solution S and water is between 7·5 and 9·2.

Iron (Vol. I, page 108). 10 ml of solution S complies with limit test B for iron (10 ppm). Use in this test 0·3 ml of thioglycollic acid R.

Heavy metals (Vol. I, page 107). 12 ml of solution S complies with the limit test for heavy metals (10 ppm). Prepare the standard using lead standard solution (1 ppm Pb) R.

Reducing substances. To 50 ml of solution S add 5 ml of dilute sulphuric acid R and 0·1 ml of 0·1N potassium permanganate. After 1 hour the pink colour has not completely disappeared.

Assay. Dissolve about 0·400 g, accurately weighed, in a mixture of 100 ml of anhydrous acetic acid R and 5 ml of acetic anhydride R. After 5 minutes add 10 drops of naphtholbenzein solution R and titrate with 0·1N perchloric acid until a persistent green colour is obtained.

1 ml of 0·1N perchloric acid is equivalent to 13·61 mg of $C_2H_3NaO_2,3H_2O$. "

Page 194. **Sodium hydroxide**

Replace the first sentence of the test for heavy metals by the following:

" Dissolve 1·5 g in 10 ml of water, neutralise with 3 ml of hydrochloric acid R and dilute to 15 ml with water. "

Page 197. **Sodium sulphate, anhydrous**

Replace the text by the following:

" Ignite anhydrous sodium sulphate (Vol. I, page 337) at 600° to 700°.

It contains not more than 0·5 per cent of water, determined by drying in an oven at 130°.

Store in a well-closed container. "

STANDARD SOLUTIONS FOR LIMIT TESTS

Page 210. Insert after " Magnesium standard solution (10 ppm Mg) ":

" **Nitrate standard solution (10 ppm NO_3)**

Dilute with water to 100 times its volume a solution containing potassium nitrate R equivalent to 1·631 g of KNO_3 in 1000·0 ml. "

Page 210. **Phosphate standard solution (5 ppm PO_4)**

Replace in the 2nd line " sodium " by " potassium ".

VOLUMETRIC ANALYSIS

REFERENCE SUBSTANCES FOR VOLUMETRIC SOLUTIONS

Page 217. **Zinc RV**

In the 5th line of the test for lead, replace " 50 ppm " by " 100 ppm ".

STANDARDISED SOLUTIONS

Page 223. **0·02N Perchloric acid**

Replace the first two lines by the following:

" Dilute 20·0 ml of 0·1N perchloric acid to 100·0 ml with anhydrous acetic acid R. Prepare immediately before use. "

MONOGRAPHS

ACIDUM BORICUM

Page 240. Delete the test for **Nitrates.**

AMYLA

Page 246. IDENTIFICATION REACTIONS

Replace test A by: " Heat to boiling for 1 minute a suspension of 1 g in 50 ml of water and cool. Starches, except for potato starch, give, after cooling, a thin and cloudy mucilage, whereas potato starch gives a thicker and more transparent mucilage. "

BELLADONNAE FOLIUM

Page 259. TESTS

Chromatography

6th line of the 4th paragraph. Replace " potassium iodobismuthate solution R " by " sodium iodobismuthate solution R ".

CODEINII PHOSPHAS

Page 275. TESTS

Morphine

Replace the last sentence by the following:

" Any yellow to orange-yellow colour which appears is not more intense than that produced when 5 ml of a 0·0025 per cent w/v solution of morphine hydrochloride R in 0·1N hydrochloric acid is treated in the same manner. "

CODEINUM

Page 278. TESTS

Morphine

Replace the last sentence by the following:

" Any yellow to orange-yellow colour which appears is not more intense than that produced when 5 ml of a 0·0025 per cent w/v solution of morphine hydrochloride R in 0·1N hydrochloric acid is treated in the same manner. "

DIGITOXINUM

Page 281. TESTS

Loss on drying

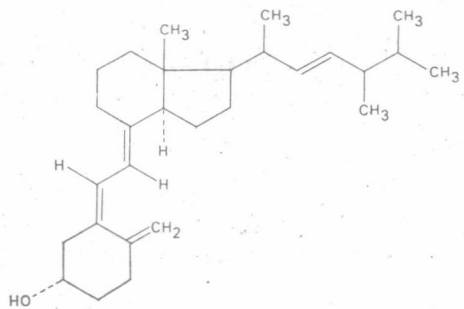
Replace the text by the following:

" **Loss on drying** (Vol. I, page 93). Not more than 1·5 per cent, determined on 0·100 g by drying in an oven at 100° to 105° for 2 hours. "

Pages287 to289. Replace the monograph ERGOCALCIFEROLUM by the following:

ERGOCALCIFEROLUM

Ergocalciferol



$C_{28}H_{44}O$ MW 396·7

Ergocalciferol is 9,10-secoergosta-5,7,10(19), 22-tetraen-3β-ol.

CHARACTERS

Colourless or slightly yellow crystals or a white or slightly yellow, crystalline powder, practically insoluble in water, freely soluble in alcohol, in ether, in chloroform and in acetone, slightly soluble in fatty oils.

IDENTIFICATION

A. Melting point (Vol. I, page 73) 113° to 116°, omitting powdering and drying.

B. Measure the extinction (Vol. I, page 83) at 265 nm of a solution in aldehyde-free alcohol R, prepared immediately before use, without the aid of heat. The specific extinction $E_{1\ cm}^{1\ per\ cent}$ is between 460 and 490.

C. Dissolve 1·00 g in alcohol R without heating and dilute to 25·0 ml with the same solvent. The specific optical rotation (Vol. I, page 80), determined immediately, is + 103° to + 107°.

D. The infra-red absorption spectrum (Vol. I, page 85) exhibits maxima which are only at the same wavelengths as, and have similar relative intensities to, those in the spectrum of ergocalciferol CRS. Prepare discs as prescribed and record the spectrum from about 2·5 to 15 µm (4000 to 667 cm^{-1}).

E. Dissolve about 10 mg in 5 ml of chloroform R and add 2 ml of acetic anhydride R and 5 drops of sulphuric acid R. A red colour develops immediately, quickly turning through violet to blue and finally green.

F. Dissolve about 1 mg in 1 ml of chloroform R and add 4 ml of antimony trichloride solution R. A yellowish-orange colour develops.

TESTS

Ergosterol Examine by thin-layer chromatography (Vol. I, page 88) using a plate 200 mm square and silicagel G R as the coating substance.

Test solution Dissolve 0·25 g of the substance to be examined in 50 ml of chloroform R.

Reference solution Dissolve 10 mg of ergosterol R in 100 ml of chloroform R and dilute 10 ml of the solution to 100 ml with the same solvent.

Apply separately to the plate, spread evenly in the form of bands 3 cm long, 50 µl of each solution and carry out the chromatographic procedure, using a mixture of 75 volumes of cyclohexane R, 20 volumes of chloroform R and 5 volumes of ethanol R as the mobile phase and allowing it to ascend 12 cm. Allow the plate to dry in air, replace it in the chamber and again allow the mobile phase to ascend 12 cm and allow the plate to dry in air. Spray with antimony trichloride solution R. The chromatogram obtained with the test solution shows a yellowish-orange area (ergocalciferol) and may show, immediately below, a violet area; the colour of the violet area is not more intense than that of the violet area in the chromatogram obtained with the reference solution.

Reducing substances and peroxides To 10 ml of a 1 per cent w/v solution in ethanol R add 0·5 ml of a 0·5 per cent w/v solution of tetrazolium blue R in ethanol R. Then add 0·5 ml of dilute tetramethylammonium hydroxide solution R. Allow to stand for exactly 5 minutes, then add 1 ml of glacial acetic acid R.

Determine the extinction (Vol. I, page 83) of the solution at 525 nm using as compensation liquid 10 ml of ethanol R treated in the same manner. The extinction is not greater than that of a solution containing 0·2 µg per ml of hydroquinone R in ethanol R, similarly treated.

STORAGE

Store in a hermetically sealed container, under vacuum or filled with an inert gas, in a cool place, in the dark.

HYOSCYAMI FOLIUM

TESTS

Page 302. **Chromatography**

In the 4th line, replace " potassium iodobismuthate solution R " by " sodium iodobismuthate solution R ".

Replace the test for **Foreign matter** by the following:

" **Foreign matter** (Vol. I, page 119) Not more than 2·5 per cent of stem with a diameter exceeding 7 mm. "

MAGNESII OXIDUM LEVIS

Page 319. Replace the Latin title MAGNESII OXIDUM LEVIS by MAGNESII OXIDUM LEVE.

TESTS

Page 319. **Solution S** Replace the first sentence by:

" Dissolve 5·0 g in a mixture of 70 ml of acetic acid R and 30 ml of water, heat to boiling for 2 minutes, cool and dilute to 100 ml with dilute acetic acid R. "

Page 320. **Heavy metals**

Replace the text by the following:

" **Heavy metals** (Vol. I, page 107) To 20 ml of solution S add 15 ml of hydrochloric acid R1 and shake with 25 ml of methyl isobutyl ketone R for 2 minutes. Separate the layers, evaporate the aqueous layer to dryness and dissolve the residue in a mixture of 1 ml of acetic acid R and 19 ml of water. 12 ml of the solution complies with the limit test for heavy metals (40 ppm). Prepare the standard using lead standard solution (2 ppm Pb) R. "

NATRII CHLORIDUM

Page 332. Delete the test for **Nitrates.**

STRAMONII FOLIUM

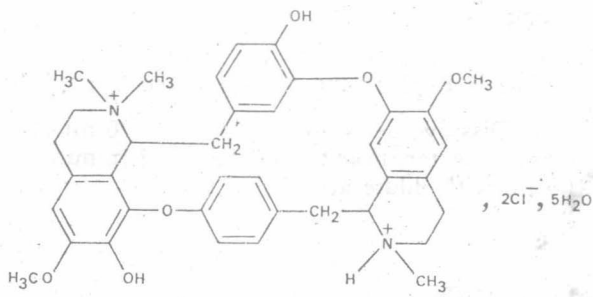
Page 369. TESTS

Chromatography

In the 6th line of the 4th paragraph, replace " potassium iodobismuthate solution R " by " sodium iodobismuthate solution R "

TUBOCURARINII CHLORIDUM

Page 379. Replace the graphic formula, the chemical formula and the molecular weight by:



$C_{37}H_{42}Cl_2N_2O_6,5H_2O$ MW 772

Page 379. Replace in the 2nd line of the definition "$C_{38}H_{44}Cl_2N_2O_6$" by "$C_{37}H_{42}Cl_2N_2O_6$".

Page 380. ASSAY

Replace in the 4th line "$C_{38}H_{44}Cl_2N_2O_6$" by "$C_{37}H_{42}Cl_2N_2O_6$".