# Solubility of Some Steroids in Water

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**The solubility of 21 steroids in water at 25° was determined and compared with previous data whenever available.**

SCATTERED data have been reported in the literature for the solubility of a number of steroids (1–8) in water. However, there seems to be no single collection of such information nor is there sufficient data, particularly for the $C_1$-dehydro corticosteroids, which have gained widespread use in pharmaceutical and medical practice during the past 10 years. A greater need for this kind of information stems from the increased interest in the dependence of drug activity upon solution concentration, which in turn is often related to drug solubility in water. A further application for such data is useful in the design of dissolution rate studies.

It is believed, therefore, that the water solubility of a number of steroids in clinical use should be reported.

## EXPERIMENTAL

Finely ground U.S.P. grade or material of equivalent quality was used for all solubility determinations. For each substance excess steroid at two initial solute concentrations, about 1 and 3 mg./ml., and 20 ml. of distilled water were added and sealed in 50-ml. glass ampuls. Each suspension was stirred for 48 hr. at 25 ± 0.1° using a Vibro-Mixer (Chemapec, Inc., Hoboken, N. J.) stirrer, which is known to effect rapid equilibration. A portion of the solution was withdrawn from the equilibrated suspension free of all solid material with a pipet fitted with a washed glass wool filter plug. The filtered solution was diluted appropriately with distilled water depending upon the quantity of substance in solution and was assayed spectrophotometrically at about 240 mμ for the conjugated A-ring ketosteroids and at about 280 mμ for the estrogenic steroids. Reference absorptivity constants were determined in a solution containing 10% methanol–90% water (v/v).

## DISCUSSION

The water solubility of 21 steroids has been determined, each at two initial suspension concentrations. In all cases, the solubility for the suspension at the lower concentration was equal to or less than that for the higher concentration. In those cases where a difference was observed, the solubility reported was calculated by extrapolation to zero suspension concentration. The coefficient of variation for replicate measurements made in this study was equal to or less than 10%. The results are summarized in Table I. Available literature data for these substances are also included.

Some generalizations can be drawn from the available data. Steroids possessing the $C_{17,21}$-dihydroxy-$C_{20}$-keto side chain, such as cortisone, hydrocortisone, prednisone, and prednisolone, show the greatest solubility in water while the solubility of the corresponding $C_{21}$ acetate esters is markedly reduced; the $C_{21}$ primary hydroxyl moiety must function importantly in the solvation process. Nevertheless, the alcoholic function of $C_{17}$ also contributes to solvation as the solubility of the $C_{20}C_{21}$-ketoalcohol, deoxycorticosterone is less than that of the dihydroxyketo analogs. The solubility of the $C_{16}$-methyl-9-α-fluoroderivatives, dexamethasone and betamethasone, is considerably less than prednisolone and is attributed to reduction of solvation about the side chain due to steric effects of the methyl substituent. The enhancing effect of the $C_{11}$ and $C_{17}$ hydroxyl group is indicated by comparing the solubility of hydrocortisone *versus* cortisone, prednisolone *versus* prednisone, and testosterone *versus* testosterone propionate.

TABLE I.—SOLUBILITY OF STEROIDS IN WATER

| Compd. | Solubility in Water, mcg./ml., 25° This Work | Lit. |
|---|---|---|
| Estradiol | 5. | 0.2 (1); 1.3 (2); 1.8 (3) |
| Ethinyl estradiol | 10. | |
| Estradiol benzoate | 0.4 | |
| Testosterone | 24. | 27 (2); 36(37°)(2); 29 (4); 125(37°) (5); 48(5) |
| Testosterone propionate | 2. | 3.7(37°) (6) |
| Ethisterone | 0.4 | |
| Methyltestosterone | 32. | 36(37°) (1) |
| Progesterone | 9. | 6.6 (2) |
| Deoxycorticosterone | 145. | 60(37°) (1) |
| Deoxycorticosterone acetate | 4. | |
| Cortisone | 230. | 280 (7) |
| Cortisone acetate | 19. | 20 (7) |
| Hydrocortisone | 285. | 280 (7) |
| Hydrocortisone acetate | 10. | 10 (7) |
| Prednisone | 115. | |
| Prednisone acetate | 23. | |
| Prednisolone | 215. | 231 (8) |
| Dexamethasone | 84. | |
| Dexamethasone acetate | 13. | |
| Betamethasone | 58. | |
| Betamethasone acetate | 30. | |

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