On the Solubilization of Steroid Hormones by Association Colloids

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For many purposes it would be advantageous if it were possible to prepare aqueous solutions of the fat-soluble steroid hormones. Hence many attempts have been made either to prepare stable high-disperse suspensions of the hormones in water or to increase the power of water to dissolve these substances. By taking advantage of the solubilizing power of association colloids we have succeeded in preparing clear stable aqueous solutions of several steroid hormones. By the end of 1947 aqueous solutions of desoxycorticosterone were obtained and half a year later we found that a similar result was possible in a varying degree in the case of testosterone, a-estradiol and desoxycorticosterone acetate. Difficulty in obtaining sufficient quantities of the pure hormones has prevented us from carrying out our investigations as originally planned. Some of the results thus far obtained are presented in the following.

Hormones can be brought into solution in a manner quite similar to that described earlier for the carcinogenic hydrocarbons, viz., by shaking them with association colloid solutions of appropriate concentration. Heating speeds up the process of solubilization. The following association colloids have thus far been studied with respect to their solubilization power: sodium oleate, sodium myristyl sulphate, sodium cholate, sodium deoxycholate, sodium dehydrocholate, sodium glycocholate, and an alkyl aryl polyether alcohol (Triton NE). The solubilities of testosterone, testosterone propionate, estrone, α-estradiol, desoxycorticosterone, and desoxycorticosterone acetate, and also hexestrol were investigated. For example, the following solutions were prepared:

**Solutions of testosterone:**
- 5 mg hormone per ml 10% sodium oleate solution;
- 10 mg hormone per ml 20% sodium myristyl sulphate solution;
- 2 mg hormone per ml 20% sodium cholate solution.

**Solutions of testosterone propionate:**
- 15 mg hormone per ml 10% sodium oleate solution;
- 35 mg hormone per ml 20% sodium myristyl sulphate solution;
- 10 mg hormone per ml 5% sodium myristyl sulphate solution.

**Solutions of estrone:**
- 1.3 mg hormone per ml 20% sodium myristyl sulphate solution.

**Solutions of a-estradiol:**
- 0.7 mg hormone per ml 10% sodium oleate solution;
- 0.8 mg hormone per ml 10% sodium myristyl sulphate solution.

**Solutions of desoxycorticosterone:**
- 14 mg hormone per ml 20% sodium cholate solution;
- 10 mg hormone per ml 10% sodium cholate solution.

**Solutions of desoxycorticosterone acetate:**
- 1.5 mg hormone per ml 10% sodium oleate solution;
- 1.8 mg hormone per ml 10% sodium myristyl sulphate solution.

**Solutions of hexestrol:**
- 12 mg hormone per ml 10% sodium oleate solution;
- 5 mg hormone per ml 10% sodium myristyl sulphate solution;
- 12 mg hormone per ml 10% sodium cholate solution.

All of these solutions are clear and stable, and withstand, for example, boiling without any separation of the hormone taking place. Solubilization is possible only when the colloid concentration exceeds the critical concentration for micelle
formation, and the amount of hormone dissolved increases with further increase in the concentration of the micellar substance. On greater dilution the hormone usually separates out sooner or later, and always when the critical concentration is approached. In this respect the various colloids differ considerably.

The association colloid solutions of the hormones give a small contact angle with lipoid surfaces. They therefore easily wet the skin and the mucous membranes, penetrate them, and transport the solubilized hormone into the tissues and cells. In this manner it is thus possible to transfer considerable amounts of hormones into the organism. Some of these solutions can be introduced by subcutaneous or intravenous injection. The investigations concerned with the latter aspect are, however, still incomplete.

The investigations are being continued.

At the beginning of our investigations we were furnished with the hormone substances required by F. Paulsen, M. D., Director of Research at the Nordiska Organon, Stockholm, and he also obtained information of our methods and results while the work was in progress. We wish to thank Dr. Paulsen.

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The Molecular Structure of N,N'-dichloropiperazine

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Structure determinations of simple derivatives of piperazine are of interest in connection with problems related to cyclohexane and other substances containing six-membered rings. The presence of two nitrogen atoms in the ring makes the number of possible configurations attainable by a given molecule greater than it is in the corresponding cyclohexane derivative. In the case of the N,N'-dichlorocompound three possible configurations based on the "chair" form of the ring have to be considered: the \( x, x \), the \( x, e \) and the \( e, e \) configuration.

We have measured the dipole moment of the substance in benzene solution, determined the unit cell and space group of the crystalline form and finally carried out an electron diffraction investigation of the vapour, based on the sector method.

Measurements of the dielectric constant of benzene solutions strongly indicate that the dipole moment is zero.

The crystals are monoclinic with the lattice constants:

\[ a = 5.83 \text{ Å}, \quad b = 5.47 \text{ Å}, \quad c = 10.98 \text{ Å}, \quad \beta = 94^\circ \]

The space group is \( C_{2h}^5 - P2_1/c \). The unit cell contains two molecules and the molecules must therefore exhibit a center of symmetry in the crystalline state.

It is interesting to compare the crystallographic data with those found in the case of the 1,4-dibromocyclohexane of m.p. 112° and the corresponding diodo-compound of m.p. 142° given in a paper published in 1932. There can be little doubt as to the isomorphism of these