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SOLUTION THERMODYNAMICS OF SOME POTENTIALLY LONG-ACTING NORETHINEDRONE DERIVATIVES III. MEASUREMENT OF AQUEOUS SOLUBILITIES AND THE USE OF GROUP FREE ENERGY CONTRIBUTIONS IN PREDICTING PARTITION COEFFICIENTS

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SUMMARY

The solubilities in water of norethindrone and 7 of its derivatives have been measured and the results compared with the values predicted by a theory of additivity of group contributions to the free energy transfer of solutes between hydrocarbon and water. Since agreement between the two is reasonable, it was shown how the aqueous solubilities of very hydrophobic derivatives can be estimated where they are too low for measurement.

INTRODUCTION

A drug may exhibit prolonged action by nature of its slow rate of metabolism and/or excretion from the body, slow rate of formation of an active metabolite, or slow release from a depot. When considering parenteral preparations, the depot may be the site of injection (subcutaneous or intramuscular tissue) or other tissues in which the drug concentrates after dissolution and distribution. If the solubility of the drug is very low in the tissue fluids and it is injected as a suspension, the rate of dissolution at the injection site is likely to be the rate-determining step in absorption and availability of the drug at the site of action. However, it is possible, with very lipophilic drugs, that rapid distribution may occur into the fatty tissues of the body. The larger the lipophilic moiety of the drug molecule, the slower will be its rate of release from these tissues (Kubinyi, 1978). If prolongation of actions is governed by release from a depot, it is evident that the physicochemical properties of the drug and the solution surrounding it are of great importance.

The norethindrone derivatives discussed in this and the previous papers (Lewis and

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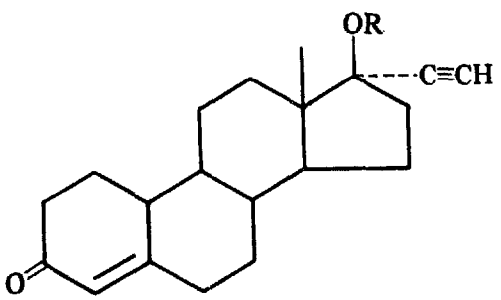
Enever, 1979a, b) have been synthesized as part of a study by the World Health Organization of long-acting systemic agents for control of fertility. The parent norethindrone and its acetate are potent progestogens, and the heptanoate ester (norethindrone enanthate) has been shown to be an effective depot contraceptive (El-Mahgoub and Karim, 1972).

In order to gain some insight into the mechanism of prolonged activity of norethindrone derivatives, a knowledge of the solution thermodynamic properties of the compounds, their rates of hydrolysis in plasma and their plasma concentrations over the period of activity are essential. Many of these data are not available, and it is the object of this paper to discuss the determination of the aqueous solubilities of some of these derivatives and correlations with solubilities predicted from group thermodynamic data.

MATERIALS AND METHODS

Materials



I Norethindrone (17-α-ethinyl-17-hydroxy-4-estrene-3-one) R=H

II Norethindrone acetate R = $-CO-CH_3$

III Norethindrone heptanoate R = $-CO-(CH_2)_5CH_3$

IV Norethindrone dimethylpropionate R = $-COC(CH_3)_2-CH_3$

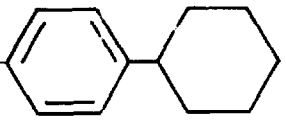
V Norethindrone trans-4-hexylcyclohexylcarboxylate R = $-CO-C_6H_{10}-(CH_2)_5CH_3$

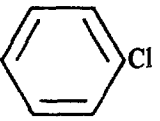
VI Norethindrone trans-3-(4-butylcyclohexyl)propionate

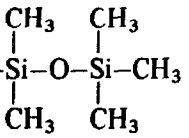
R = $-CO-(CH_2)_2-C_6H_{10}-(CH_2)_3CH_3$

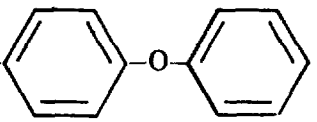
VII Norethindrone benzoate R = $-CO-C_6H_5$

VIII Norethindrone biphenyl-4-carboxylate R = $-CO-C_6H_4-C_6H_5$

IX Norethindrone 4-cyclohexylbenzoate R = –CO– 

X Norethindrone-6-(4-chlorophenyl)-hexanoate R = –CO–$(CH_2)_5$– 

XI Norethindrone pentamethyldisiloxyl ether R = 

XII Norethindrone 4-phenoxybenzoate R = –CO– 

XIII Norethindrone bicyclohexyl-4-carboxylate R = –CO– 

Compounds I and II were obtained from Serva Feinbiochemica and Compound III from Schering A.G. Berlin. The remaining compounds were obtained through the World Health Organization from the following principal investigators, who synthesized them:

Dr. A. Shafiee, College of Pharmacy, Tehran, Iran	Compounds V, VI, VIII, IX, XIII
Professor P.N. Natarajan, Department of Pharmacy, University of Singapore	Compounds VII, XII
Dr. J.E. Herz, Instituto Politecnico Nacional, Mexico 14	Compounds IV, XI
Dr. G. Krakower, Department of Chemistry, Bar Ilam University, Ramat-Gan, Israel.	Compound X

Distilled water was produced from a quartz glass double still. 2,2,4-Tritmethylpentane (iso-octane) was of spectroscopic grade from British Drug Houses Limited. Analar Methanol was also obtained from British Drug Houses Limited.

Methods

A form of phase solubility analysis was used to determine the aqueous solubilities of the more soluble norethindrone and norethindrone acetate. Crystals of each compound were equilibrated with known quantities of double-distilled water and iso-octane (Higuchi, 1977) at constant temperature. The hydrocarbon acted as a catalyst, since the steroid dissolved rapidly in such a lipophilic solvent and was quickly distributed into the aqueous layer. If such a technique had not been used, equilibration would have taken several weeks, since phase solubility analysis involves the dissolution of all impurities in the crystals as well as formation of a saturated solution of the main component. It would not have been possible to use a vast excess of the compound to provide a large surface area and

facilitate the rate of dissolution since an unknown quantity of impurity might be present which, if more soluble, could exceed the amount of main component in solution.

The saturated aqueous solution was then filtered through a 0.45 μm Millipore cellulose acetate membrane that had previously been washed with some of the solution to remove soluble impurities. The filtrate was suitably diluted with ethanol and the steroid concentration determined by measuring the absorbance of the alcoholic solution at 240 nm using a Pye-Unicam SP1800 spectrophotometer. The method utilizing a lipophilic solvent worked well for aqueous solubilities in excess of 1 μg/g of solvent. The remainder of the compounds had very low aqueous solubilities – ranging from 1 μg/g down to the order of 10^{-5} μg/g. In these circumstances, the concentration of steroid in the iso-octane layer would normally be quite high and in the aqueous layer very low. During separation of the two phases, the slightest contamination of the aqueous layer with iso-octane could lead to more than a 10-fold error in the measured aqueous solubility. Another difficulty would be that the absorbance values of the aqueous solutions would be too low to measure without a concentration step. Therefore, the aqueous solubilities of norethindrone heptanoate (III), dimethylpropionate (IV), benzoate (VII), biphenyl-4-carboxylate (VIII), pentamethyldisiloxyl ether (XI) and 4-phenoxybenzoate (XII) were determined in the following manner:

An excess of each compound (10–30 mg in 20 g of double-distilled water) was equilibrated for 2–4 weeks at constant temperature. Although this period is not sufficient to attain equilibrium, it was long enough to obtain a saturated solution of the main component. Subsequently, the solution was filtered through a 0.45 μm Millipore cellulose acetate membrane, taking precautions to avoid adsorption of the steroid onto the membrane (Batra, 1975). Adsorption effects were expected to be significant with these considerably more hydrophobic compounds, especially when large volumes of saturated aqueous solution were passed through the filter causing it to swell slightly. Instead of attempting to saturate the filter prior to filtration, a fresh filter was used for each aqueous sample. Leaching of additives from the membrane also occurred, but these impurities did not affect the subsequent analysis of the steroid.

The total filtrate volume was extracted with 2 ml of iso-octane which was subsequently evaporated to dryness and the steroid dissolved in 80% v/v methanol in water in which either medroxyprogesterone or medroxyprogesterone acetate had been dissolved to act as an internal standard. The steroid concentration was then determined by high performance liquid chromatography using a Cecil Instruments CE212 ultraviolet monitor and CE210 liquid chromatograph equipped with a 250 mm column containing microparticulate silica coated with an octadecylsilyl bonded phase (Whatman, Partisil 10-O.D.S.). The mobile phase was 80% v/v aqueous methanol, and the detection wavelength was 240 nm. The injection volume was approximately 200 μl which normally accounted for half the total steroid obtained by extraction. The resulting chromatograms revealed that concentrations of impurities, having shorter retention times that the steroids, were in some cases much greater than the compounds under investigation. The peaks obtained for the steroids were small in the majority of cases, and in fact that of norethindrone biphenyl-4-carboxylate, the most insoluble compound used, was just detectable. It was estimated that the maximum sensitivity of this technique was of the order of 1 ng/g of solvent for these steroids.

The remainder of the steroids had aqueous solubilities that were too low to measure even by this technique, and it was necessary to predict their solubilities from a knowledge of their solubilities in iso-octane and estimated partition coefficents between iso-octane and water.

RESULTS AND DISCUSSION

Fig. 1 shows the aqueous solubilities of norethindrone and norethindrone acetate at temperatures between 5 and 55°C plotted as log (solubility) against temperature. It is evident from these graphs that the enthalpies of solution in water increase with temperature. Such a phenomenon has been observed with other substances (Shinoda, 1977). The measured aqueous solubilities of the remaining steroids at 25°C are shown in Table 1.

Provided correction is made for the lattice energy of the crystal, aqueous solubilities can be analyzed in terms of molecular structure of the solute. The simplest way to achieve this is to calculate the partition coefficients of the compounds, since the free energy of transfer of an organic molecule between two solvents can be approximated to the sum of the contributions for all the groups present. In this work the mass fraction concentration scale has been chosen which, for partition coefficients at low concentrations, is equivalent to the molality scale. A large number of data on group contributions have been collected by Davis et al. (1974) and this discussion makes use of many of these and adopts a similar approach. Davis (Davis et al., 1974; Davis, 1973a, b) gives data in terms of the mole fraction concentration scale, which he prefers, on theoretical grounds, to the molarity scale employed by Leo et al. (1971) in their lengthy table of measured partition coefficients. We do not believe that it has yet been definitely shown that either concentration scale is the more correct on theoretical physicochemical grounds. For the practical purposes of summing group contributions to determine the free energies of transfer, it does not matter which scale is used, although the free energy values of certain groups are concentration scale dependent.

In this discussion, to show which concentration scale is being used, we have used the

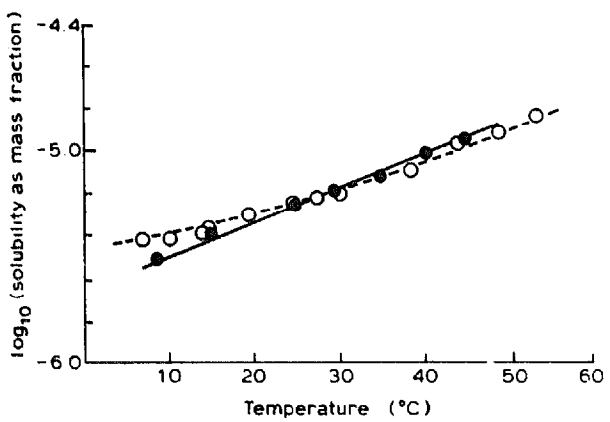


Fig. 1. Solubilities of norethindrone (o) and norethindrone acetate (•) in water over a range of temperature.

TABLE 1

MEASURED AND PREDICTED SOLUBILITIES OF NORETHINDRONE DERIVATIVES AT 25°C

Compound	log measured aqueous solubility ($\log C^0_{aq}$) (mass fraction scale)	log activity coefficient in iso-octane ($\log \gamma^{\infty}_m$)	log predicted aqueous solubility (mass fraction scale)
Norethindrone (I)	−5.25	−4.52	(−4.65) [b]
Norethindrone acetate (II)	−5.25	−2.92	(−5.44) [b]
Norethindrone heptanoate (III)	−7.22	−1.94	−7.48
Norethindrone dimethypropionate (IV)	−7.52	−3.68	−7.57
Norethindrone trans-4-hexylcyclohexyl carboxylate (V)	[a]	−2.33	−10.66
Norethindrone trans-3-(4-butylcyclohexyl)propionate (VI)	[a]	−2.03	−10.36
Norethindrone benzoate (VII)	−8.09	−4.24	−7.64
Norethindrone biphenyl-4-carboxylate (VIII)	−8.43	−3.86	−8.89
Norethindrone 4-cyclohexylbenzoate (IX)	[a]	−3.47	−9.77
Norethindrone 6-(4-chlorophenyl)-hexanoate (X)	[a]	−3.96	−11.24
Norethindrone pentamethyldisiloxyl ether (XI)	−6.99	−0.94	(−6.06) [c] −7.10
Norethindrone 4-phenoxybenzoate (XII)	−7.15	−2.57	−7.47
Norethindrone bicyclohexyl-4-carboxylate (XIII)	[a]	−2.57	−11.10

[a] Aqueous solubilities too low to measure.
[b] Log K_m predicted form thermodynamic group contribution of the whole molecule.
[c] Using alkylsilane data.

subscripts 'x' and 'm' for the mole fraction and mass fraction scales, respectively. Where there is no subscript, the quantity is independent of concentration scale.

The partition coefficients may be calculated from the solubilities of the compounds in iso-octane and water using the following approach:

$$\mu^{(1)} = \mu^s + RT \ln \gamma^{(1)} c^{(1)} \text{ and } \mu^{(2)} = \mu^s + RT \ln \gamma^{(2)} c^{(2)} \quad (1)$$

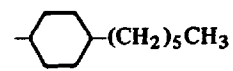
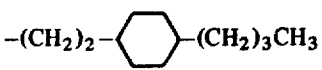
where $\mu^{(1)}$, $\mu^{(2)}$ and μ^s are the chemical potentials of the solute in solvents 1, 2 and the solid state, respectively, and $\gamma^{(1)}$ and $\gamma^{(2)}$ are the activity coefficients in solvents 1 and 2 at concentrations $c^{(1)}$ and $c^{(2)}$, respectively.

If the solvents are very dilute $\gamma^{(1)} \to \gamma^{(1)\infty}$, $\gamma^{(2)} \to \gamma^{(2)\infty}$, and if $c^{(1)} = c^{(2)}$, the standard free energy of transfer

$$\Delta\mu^t = \mu^{(2)} - \mu^{(1)} = RT \ln \frac{\gamma^{(2)\infty}}{\gamma^{(1)\infty}} = -RT \ln K \quad (2)$$

TABLE 2

CALCULATION OF LOG K VALUES FOR ALIPATHIC NORETHINDRONE DERIVATIVES AND COMPARISON WITH THOSE ESTIMATED FROM SOLUBILITY DATA IN ISO-OCTANE AND WATER AT 25°C

Compound	Substituent group	log K_m (acetate)	Extra carbon atoms (n)	n log F (CH_2)	Ring closure correction	Branching correction	Predicted log K_m	log K estimated from solubility data
I	$-H$						(0.10) [b]	0.73
II	$-CH_3$		0	0	0	0	(2.52) [b]	2.40
III	$-(CH_2)_5CH_3$	2.40	5	3.15	0	0	5.55	5.28
IV	$-C(CH_3)_3$	2.40	3	1.89	0	−0.40	3.89	3.84
V		2.40	11	6.93	−0.80	−0.20	8.33	[a]
VI		2.40	11	6.93	−0.80	−0.20	8.33	[a]
XIII		2.40	11	6.93	−1.60	−0.20	7.53	[a]

[a] Aqueous solubilities too low to measure.

[b] Log K_m predicted from group contributions of the whole molecule.

where K is the partition coefficient If the solutions are dilute, K approximates to the ratio of the solubilities of the compound in the two media. However, if one of other solubility exceeds 10^{-3} mass fraction, correction must be made for non-ideality. Values of $\log \gamma^{\infty}$ for solution of iso-octane have previously been estimated (Lewis and Enever, 1979b) and are listed in Table 1. Table 2 gives values for log K_m calculated from the solubility data for the aliphatic derivatives.

With the exception of norethindrone and norethindrone acetate, direct measurement of partition coefficients has proved impracticable because of the high hydrophobicity of the derivatives. The data obtained for norethindrone and its acetate are shown in Fig. 2.

The process: norethindrone acetate (iso-octane) → norethindrone acetate (water) is observed to be exothermic, as is usual for a hydrophobic molecule partitioned between water and a hydrocarbon solvent. There is still considerable doubt, in the absence of a reliable model for liquid water, as to the cause of this effect and the significance of the large positive standard molar entropy change of the process (Shinoda, 1977; Ben-Naim, 1978b; Davis et al., 1974). The entropy change depends on the standard concentration employed. Transferring from the mole fraction to the molar concentration scales decreases the entropy of transfer in the above case by 2.2 R. The entropy of transfer of a methylene group is not concentration scale-dependent which makes its value useful in discussions of the hydrophobic effect in spite of the difficulties of determining its value accurately.

For those compounds whose aqueous solubilities were too low to measure, it was not possible to determine partition coefficients, and it was necessary to predict them by use

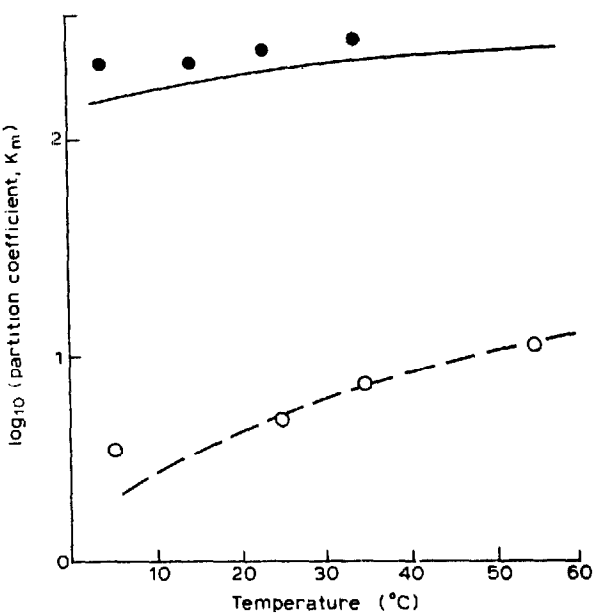


Fig. 2. Relation between logarithm of parition coefficient and temperature for norethindrone (o) and norethindrone acetate (•). The plotted points represent the experimentally determined partition coefficients, whilst the lines represent partition coefficients calculated from the ratios of solubility in iso-octane to that in water.

of the group contribution approach. In fact, this approach has been applied to all compounds so that the validity of the procedure could be checked by comparison with experimentally measured values.

Prediction of partition coefficients

(i) Aliphatic derivatives of norethindrone

The measured partition coefficient of norethindrone acetate was $10^{2.40}$ at 25°C. Davis (1973a) has summarized the evidence that addition of a methylene group to a molecule increases the partition coefficient by a constant factor, which for the hydrocarbon–water system is $10^{0.63}$. This represents a free energy of transfer for the methylene group of 3.58 kJ mol^{-1}. The partition coefficient of norethindrone heptanoate (III) can therefore be derived from that of the acetate by taking into account the contribution of 5 methylene groups.

For molecules containing branched chains or alicyclic groups, the free energies of transfer from hydrocarbon to water are less than their straight chain equivalents. A correction can be made for each branch in the chain by a factor of $10^{-0.20}$ and each ring closure by use of a factor of $10^{-0.80}$ in K. The calculation of log K_m for each compound is shown in Table 2.

From the measured values of log $\gamma^{\infty}{}_m$ in iso-octane given in Table 1, aqueous solubilities can be predicted using Eqn. 2. Since the solution in water is dilute, Eqn. 2 becomes:

$$K = (\gamma^{(1)\infty} C^0{}_{aq})^{-1} \tag{3}$$

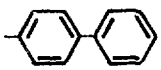
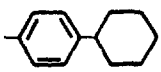
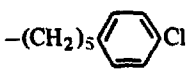
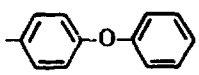
where $C^0{}_{aq}$ is the solubility in water and $\gamma^{(1)\infty}$ is the activity coefficient in iso-octane at infinite dilution. This equation holds provided the mutual solubility of water and iso-octane is low. Serious deviations from Eqn. 3 occur in the case of octanol and water. The calculated values of logarithm of aqueous solubility for these aliphatic derivatives are shown in Table 1.

(ii) Aromatic derivatives of norethindrone

In the calculation of log K_m outlined in Table 3, it is apparent that values listed for the group contribution of the methylene group and the corrections for ring closure and branching are independent of the concentration scale employed. This arises from the fact that the group contribution of the methylene group is obtained by subtraction of the free energy of transfer of the parent compound from the substituted compound. The same will be true for any group that forms two valency bonds upon incorporation in a molecule (bifunctional group). Change in concentration units would, of course, affect the value of log K obtained for norethindrone acetate – the parent compound in this calculation. In fact, if attempts are made to derive a value for the free energy of transfer of a monofunctional group such as a methyl group, it will be found that the value obtained again depends on the concentration scale used. Thus the standard partial molar free energy of transfer is not entirely a measure of the differences in solvation of a molecule in water and a hydrocarbon solvent, and this has led to some doubt as to the proper concentration scale to use and to the value of the group contribution for the methyl group

TABLE 3

CALCULATED LOG K VALUES FOR AROMATIC NORETHINDRONE DERIVATIVES AND COMPARISON WITH THOSE ESTIMATED FROM SOLUBILITY DATA IN ISO-OCTANE AND WATER AT 25°C

Compound	Substituent group	Predicted log K_m	log K_m estimated from solubility data
VII		3.3	3.9
VIII		4.9	4.6
IX		6.3	[a]
X		7.3	[a]
XII		4.9	4.6

[a] Aqueous solubilities too low to measure.

(Davis, 1973b; Hansch, 1971; Ben-Naim, 1978a).

However, Davis (1973a) has clarified the group value for a methyl group attached to an aliphatic compound. Using the mole fraction concentration scale, he obtained a number of values that were in good agreement and, using alkane data, the group value in log K_x for a methyl group is 1.46. With this information, group values for aromatic groups can be combined with the measured partition coefficient or norethindrone acetate. Unfortunately, reliable value for such groups are not available, nor are good values for the methyl group attached to an aromatic ring. Davis (1973a) stated that whereas the group value for a methyl group at the end of an alkyl chain is greater than that of a methylene group, the group value of a methyl group attached to an aromatic ring is the same as a methylene group. Unfortunately, he used a different method of calculation of the group values in each case, and by taking the difference in logarithm of partition coefficient of, for example, toluene and benzene, he has in effect calculated a group value for methylene and not the methyl group. In the absence of other data, we have therefore assumed that a methyl group attached to an aromatic ring has the same group value as an aliphatic methyl group. With this assumption, a group value can be derived for the $-C_6H_4-$ group using solubility parameter data available for 1,4-dimethylbenzene (Hildebrand et al., 1970).

Using the mole fraction scale, the logarithm of the activity coefficient of 1,4-dimethylbenzene at infinite dilution in aqueous solution, log γ^{∞}_x, has been found to be 4.49 (Tsonopoulis, 1970). The activity coefficient at infinite dilution in iso-octane can be estimated from solubility parameters, δ, which are listed for a number of simple aromatic

hydrocarbons, since

$$\log \gamma^{\infty} = \frac{V_2(\delta_1 - \delta_2)^2}{2.303\ RT} = 0.022 \quad (4)$$

where δ_2 is the solubility parameter of 1,4-dimethylbenzene (18.0 $MPa^{1/2}$) and V_2 is its molar volume (1.24×10^{-4} m^3), whilst δ_1 is the solubility parameter of iso-octane (17.0 $MPa^{1/2}$) (Hildebrand et al., 1970).

Thus lof $K_x = 4.49 - 0.022 \approx 4.47$ (mole fraction scale).

If the group contributions for two methyl groups are subtracted from this log K_x value, a group value of 1.55 is obtained for the $-C_6H_4-$ group. Since this group is bifunctional, the value is independent of the concentration scale used. Therefore the logarithm of the partition coefficient of norethindrone benzoate (VII) can be calculated from:

$$\log K_m(\text{norethindrone benzoate}) = \log K_m(\text{norethindrone acetate}) - \log F(CH_2) + \log F(-C_6H_4-) = 3.32 \text{ (molality or mass fraction scale)} \quad (5)$$

By similar reasoning, the partition coefficient of norethindrone biphenyl-4-carboxylate (VIII) between iso-octane and water can be calculated to be $10^{4.87}$. Aqueous solubilities can then be calculated for both these compounds using Eqn. 3, and the values obtained are shown in Table 1. In this approach no allowance is made for interactions between the π electrons of the carbonyl group and the phenyl group, which may affect the hydrogen bonding capacity of the benzene ring. Values of the partition coefficients, between n-octanol and water, calculated according to the molar concentration scale and reported by Leo et al. (1971), are 2.12 for methylbenzoate and 0.18 for methyl acetate. These indicate that the increment in both log K_m and log K_x between norethindrone acetate and norethindrone benzoate should be 1.84. This should be similar for distribution between water and iso-octane as group free energy values for the hydrophobic portion of the molecule are not greatly solvent-dependent. This indicates a solubility of $10^{-8.5}$, lower than the measured value. If this method is applied to norethindrone biphenyl-4-carboxylate (VIII) using the octanol–water data (Leo et al., 1971),

$$\log K_x(\text{biphenyl}) = 4.98$$
$$\log K_x(\text{benzene}) = 3.08$$

a K_m value of $10^{6.14}$ and a water solubility of 10^{-10} are predicted. The reason for the discrepancy between the two methods is unclear.

Estimation of log K_m for norethindrone 4-cyclohexylbenzoate (IX) presents no problems since the necessary data are available for aliphatic derivatives (Table 2).

$$\log K_m(\text{norethindrone 4-cyclohexylbenzoate}) = \log K_m(\text{norethindrone acetate}) + 5 \log F(-CH_2-) + \log F(-C_6H_4-) + \log F(\text{ring closure}) = 6.30 \quad (6)$$

This can be modified to take account of the experimental value for norethindrone benzoate to give a value of 7.43, and the predicted solubility altered accordingly.

For the norethindrone-6-(4-chlorophenyl)hexanoate (X), data are available for the effect of substitution of an aromatic hydrogen by a chloride atom (Davis, 1973c). The best group value appears to be 0.73 which leads to an estimate of 7.28 for log K_m of the ester.

In order to calculate log K_m for norethindrone 4-phenoxybenzoate (XII) a group value for the ether linkage is required, since there are no literature data on the partitioning of diphenyl ether between iso-octane and water. Davis et al. (1974) quote various values for the ether linkage. It is strongly dependent on the nature of the attached groups and the non-aqueous solvent. The more hydrophobic the molecule the less is the interaction with water. Data for diphenyl ether reported by Leo et al. (1971) indicate a contribution of 0.32 for octanol/water, (demonstrating shielding of the oxygen by the phenyl groups) but the value for iso-octane/water is likely to be negative (i.e. favouring transfer to water). By analogy with the results quoted by Davis et al. (1974) for the methoxy group between cyclohexane and water and octanol and water the group value for alkanes might be less than that for octanol by approximately 0.3. The F value for (–O–) in (XII) is taken as 0.0 but it must be recognized that this can only be approximate. The predicted partition coefficient is thus $K_m = 10^{4.9}$ and the predicted aqueous solubility becomes $10^{-7.47}$.

There is an even greater lack of data for the partition coefficients of compounds containing silicon and no data for alkyl siloxanes. It was assumed, as a first approximation, that the side chain is equivalent to a substituted ether with carbon replacing silicon atoms. In this case:

$$\log K_m(\text{norethindrone pentamethyldisiloxyl ether}) = \log K_m(\text{norethindrone}) - \log F(-OH) + \log F(CH_3) + 5 \log F(CH_2) + 4 \log F(\text{branching}) + 2 \log F(-O-)$$
$$= 0.8 + 3.45 + 1.46 + 3.15 - 0.80 - 2.00 = 6.16 \quad (7)$$

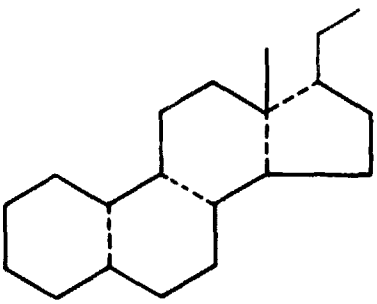
Data are available for various alkyl silanes distributed between n-octanol and water (Lee, 1967). There are some apparent inconsistencies in the results for the higher members of the series (octyldimethylsilane and octyltrimethylsilane), but from the remaining data we estimate group values on the mole fraction scale of log $F_x(-SiMe_3) \approx 2.13$ and log $F(-SiMe_2-) \approx 1.12$. We obtain using the measured value and data taken from Davis et al. (1974).

Norethindrone – measured value of log K_m =	0.80
$-\log F_x(-OH)$ =	3.45
$-\log F_x(-SiMe_2)$ =	2.13
$+\log F(-SiMe_3)$ =	1.12
$+2 \log F(-O-)$ =	–2.00
Total – log K_m	5.50

The group value for (–O–) has caused difficulty, as there are few data on ethers in the literature, and in this case the oxygens are shielded from interaction with water by the methyl groups. For a phenylmethyl ether the group value is around –1.0 and for the more shielded oxygen in diphenyl ether it is around zero (see above). We have taken the

value to be −1.0, expecting considerable shielding to operate.

Lastly we will attempt to calculate the partition coefficients of norethindrone and norethindrone acetate between hydrocarbon and water directly. Drawing the pregnane-molecule as in A below we see that the partition coefficient of norethindrone can be calculated as follows:



A

$F(CH_2) \times 20$	= 12.60
Methyl group correction × 2	= 1.66
Ring closures (4)	= −2.88
Unsaturation	= −2.21
Hydroxyl group replacing –H	= −4.28
Ketone group replacing CH_2	= −3.99
Log K_x(estimated)	= 0.90

Data were derived from Davis et al. (1974) and from Leo et al. (1971). In the case of the allowances for ring closure, values for group contribution to the log activity coefficient are used. The approximation that these are equal to the group contribution to the partition coefficient is good for partition between saturated hydrocarbon and water, but not for partition between benzene or octanol and water. The measured partition coefficient (mole fraction scale K_x) is $10^{1.53}$, so agreement between experiment and theory is good (within 4 kJ mol^{-1}).

For norethindrone acetate the procedure is similar. However, there are no data for esters in saturated hydrocarbons. Using the data of Leo et al. (1971) for ethyl acetate and solubility parameter theory (Barton, 1975), a group value for $-\overset{\overset{O}{\|}}{C}-O-$ in iso-octane may be derived.

log K_x norethindrone (calculated value)	= 0.90
F(–OH)–F(–H)	= 4.28
$F(-O-\overset{\overset{O}{\|}}{C}-)$	= −2.49
$F(CH_2)$	= 0.63
	3.32 for norethindrone acetate

The measured value of log K_x is 3.20 (log K_m = 2.40).

The data for the aliphatic compounds I–IV show good agreement between measured and predicted values (Tables 1 and 2), although the very good agreement between the two values for norethrindrone acetate is probably fortuitous. As has been shown above, there is some doubt about the best data to use for the group contributions of the benzene ring. If its hydrophobic effect in aromatic esters is assumed similar to that of the benzene ring in simple aromatics, then agreement with experiment is reasonable for those compounds where it was possible to measure the aqueous solubility. The biphenyl-4-carboxylate (VIII) has a very low solubility but the measured solubility is still higher than predicted.

The results therefore indicate that the solubilities predicted for the compounds with long alkyl groups are most likely good estimates. No allowance is made however, for intramolecular hydrophobic interaction, with the side chain weakly bonded to the steroid nucleus, thus lowering the surface area at the expense of a loss in the conformation entropy. Where this occurs the solubility in water would increase. There is evidence for such an increase in solubility over the expected values in alkanes higher than n-dodecane (Nelson and de Ligny, 1968). However, studies of circular dichroism of alkyl esters of hydrocortisone in aqueous solution (O'Neill, personal communication, 1978) show evidence for an extended conformation of the side chain. Because of the simple nature of the interactions between hydrocarbons and solute molecules these appear more suitable than n-octanol for the prediction of aqueous solubilities by the methods described above. It is clear that there is a shortage of useful measurements of partition coefficients between water and a hydrocarbon, in particular of esters and ethers. It is in relatively polar molecules that the partition coefficient between iso-octane and water differs greatly from the octanol–water values, and although linear relationships have been shown (Leo et al., 1971) for calculating partition coefficients in one system from the octanol–water values, they are not at all reliable for calculation of group values.

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