ty in this series of compounds is the bis(β-phenethyl) ketone system. Previous studies have shown that the ketone alone is inactive, and data are presented here showing that monosubstituted compounds are either inactive (17) or less active (18) than the symmetrically substituted ketone. The activity of the basic structure may be modulated by substitution of the α or β carbons, aromatic substitution, or modification of the ketone moiety.

Highest activity is seen when some substitution is present only at both α carbons (*e.g.*, 1 and 6). Removal of α substituents (11) or introduction of a more rigid framework as has been previously reported[1] (*e.g.*, 2,6-dibenzylcyclohexanone) leads to loss of activity. This pattern of high activity being associated with moderate steric hindrance at the α carbon suggests that there is a correlation between conformation and activity, and studies are underway to examine this relationship in more detail.

Reduction (*e.g.*, 2) or substitution of the aromatic ring lowers both hypocholesterolemic and estrogenic activity but at different rates. Since the estrogenic effect may be unrelated to the hypocholesterolemic activity and is an undesirable side effect of the hypocholesterolemia, an attempt was made to exploit this pattern.

Compounds **22, 25, 27, 29, 32,** and **34** show this differential effect of substitution upon the two biological activities. Of particular interest is compound **34,** which has a much lower estrogenic activity but retains some hypocholesterolemic effect. This raises the possibility that the estrogenic activity is due to a metabolite of 2,8-dibenzylcyclooctanone whose bioactivation is blocked by para substitution. Accordingly, the 4-chloro, 4-fluoro, and 4-hydroxy analogs are of some interest. Preliminary synthetic efforts have shown that the usual procedures are not successful because of the higher solubility of the bisylidenes and consequent difficulties in isolation. Some success has been achieved with an alternate route, which will be the subject of a later communication.

The addition of any group to the benzylic carbon (**5, 8, 9, 10, 31**) lowers activity, as does restricting rotation about the α–β bond (**7, 21**). This is in congruence with our earlier finding that the intermediate ylidenes are devoid of activity.[1]

The carbonyl moiety may be reduced (14) or removed (16). Hypocholesterolemic activity drops upon reduction to the alcohol and is lost entirely when the carbonyl carbon is completely saturated. It is possible that carbonyl derivatives (*e.g.*, oximes) or related moieties such as the ester function would show activity. Synthetic difficulties have so far precluded the preparation of such analogs.

Table IV. Estrogenic Activity in Ovariectomized Sprague–Dawley Rat

	N	% control uterine wt	*P*
Control (1% CMC)	21	100 ± 23	
1	13	260 ± 22	0.001
6	8	148 ± 17	0.005
25	8	131 ± 20	0.050
27	8	143 ± 26	0.025
29	8	74 ± 6	n.s.
34	8	72 ± 16	n.s.
Ethinylestradiol (10 μg/kg)	13	259 ± 9	0.001

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A Hansch Analysis of the Anabolic Activities of Some Nandrolone Esters

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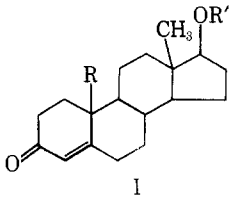
The anabolic activities in the rat of the butyrate to undecanoate normal fatty acid esters of nandrolone have been determined. Two peaks of activity were observed in plots of organ weight against time, for each ester, and assigned to release into the blood from the site of injection and from body fat, respectively. Anabolic activities were measured as increase in weight of levator ani over control weight, multiplied by duration of response. Solubilities in water and in ethyl oleate have been determined and distribution coefficients calculated. A binomial relationship was obtained between log anabolic activity and log ethyl oleate–water distribution coefficient. Similar equations were derived from the results of other authors.

The androgenic activity of testosterone can be enhanced and prolonged by esterification[1] and the times of maximum effect of the lower fatty acid esters, in the rat, are logarithmically related to the logarithms of their distribution coefficients.[2] Nandrolone decanoate (17β-decanoxyest-4-en-3-one) (Table I) has been shown pharmacologically to have a prolonged anabolic effect.[3] It is compared here with other nandrolone esters to determine if its enhanced biological activity is due to a favorable oil–water distribution coefficient.

Methods

Preparation of Esters. Nandrolone and nandrolone decanoate were gifts from Organon Laboratories, Ltd. The remaining esters

Table I. Characterization and Solubilities



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Compound	R	R′	Mp,[b] °C	Solubility (% w/w)[c] Ethyl oleate	Water (×10⁴)	Analyses[d]
Testosterone[a]	CH_3	OH				
Esters of nandrolone						
Butyrate	H	$OCO(CH_2)_2CH_3$	73	34.6 (1.9)	5.03 (0.02)	C, H
Oxime			60			C, H, N
Hexanoate	H	$OCO(CH_2)_4CH_3$	Oil	63.1 (1.3)	3.28[e]	C, H
2,4-Dinitrophenylhydrazone			118			C, H, N
Heptanoate	H	$OCO(CH_2)_5CH_3$	Oil	50.2 (3.1)	1.87[e]	
Octanoate	H	$OCO(CH_2)_6CH_3$	Oil	65.3 (1.3)	1.07[e]	C, H
2,4-Dinitrophenylhydrazone			120			C, H, N
Nonanoate	H	$OCO(CH_2)_7CH_3$	40–40.5	42.1 (0.4)	0.926 (0.001)	C, H
2,4-Dinitrophenylhydrazone			118			C, H, N
Decanoate	H	$OCO(CH_2)_8CH_3$		53.2 (0.9)	0.664 (0.005)	
Undecanoate	H	$OCO(CH_2)_9CH_3$		88.3 (2.6)	0.602 (0.021)	

[a]Nomenclature for esters as for nandrolone. [b]Melting points are uncorrected and are quoted for new compounds only. [c]The figures in parentheses represent 95% confidence limits. [d]Analytical results are within ±0.4% of theoretical values. [e]Estimated.

were prepared *via* the acid chlorides. Analytical data are given in Table I.

Determination of Biological Activities. Male albino rats (Tuck, 40–60 g) were castrated under ether anesthesia and treatment began 2 weeks later. The esters were dissolved in ethyl oleate for injection into rats. At various time intervals following the injection of 0.1 ml of either ethyl oleate or the nandrolone ester solution into the left gluteus muscle, groups of three animals were killed. The levator ani muscles were immediately removed and weighed. Duplicate weighings were carried out after each time interval. Four dose levels between 250 μg and 1 mg were tested for each ester.

Determination of Solubility in Water. An excess of ester was stirred with water at 37° until a saturated solution was obtained. Exactly 5 l. was filtered off and evaporated to dryness under vacuum on a rotary evaporator. The residue was taken up in cyclohexane and the concentration of the saturated solution calculated from the extinction of the extract, measured at 231 nm. The procedure could not be used with esters having melting points below 37° because excess solute could not be removed by filtration.

McAulliffe[4] has shown that the aqueous solubilities of a homologous series of hydrocarbons are logarithmically related to molar volume. This was tested for the system under investigation by examination of the corresponding testosterone esters, which are mainly solids at 37°. A good linear plot of log solubility against molar volumes was obtained, indicating that the solubilities of the liquid nandrolone esters could be estimated reliably by interpolation of the plot of the log solubilities of the four solid nandrolone esters against molar volume. Both graphs are shown in Figure 1.

Determination of Solubilities in Ethyl Oleate. The percolation process for preparation of saturated solutions[5] could not be employed with the liquid esters because of filtration difficulties. Saturated solutions were prepared in a tube, sealed at one end, 15 cm long and 2.5 cm in diameter, in which the liquid in excess could be induced to sink completely to the bottom, leaving a clear supernatant. The process was compared with the percolation method, using testosterone propionate. There was only ±0.5% variation between the two methods in two sets of 12 results. Concentrations were determined by ir spectrophotometry.[6]

Solubilities in water and ethyl oleate are given in Table I. Aqueous solubilities are the means of at least three determinations. Those in ethyl oleate are the means of eight determinations. Distribution coefficients were calculated as the ratio of the solubilities in the two solvents.

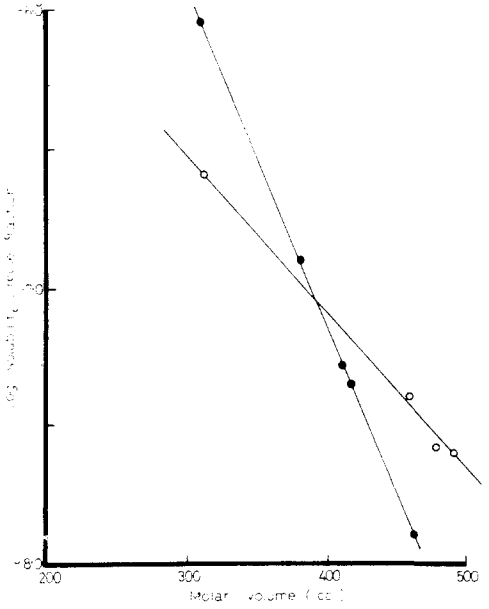

Figure 1. Relationship between molar volumes and aqueous solubilities: ●, testosterone series; ○, nandrolone series.

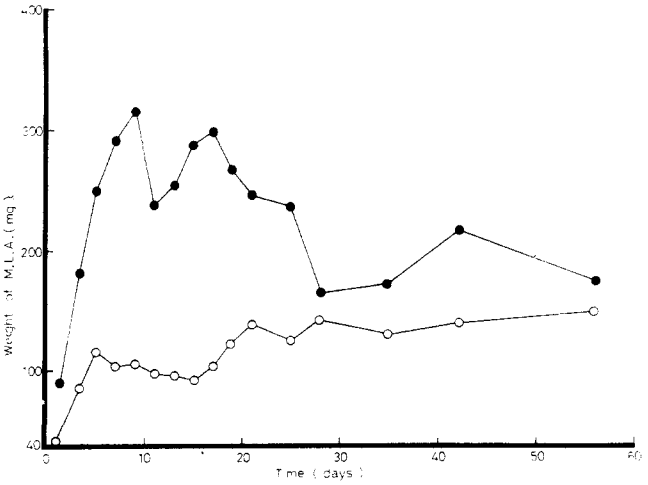

Figure 2. Effect of nandrolone nonanoate on levator ani: ●, 1 mg of nandrolone nonanoate; ○, control.

first maximum

$$\log TM = 0.270\ (0.061) \log P - 0.486\ (0.342) \quad n = 7 \quad r = 0.882 \quad s = 0.070 \qquad (1)$$

$$F_{1,5} = 120.3\alpha\ (0.001) = 47.18$$

second maximum

$$\log TM = 0.219\ (0.028) \log P - 0.0153\ (0.157) \quad n = 7 \quad r = 0.958 \quad s = 0.030 \qquad (2)$$

$$F_{1,5} = 446.2\alpha\ (0.001) = 47.18$$

Determination of Molar Volumes. A capillary tube was calibrated by measuring the length of given weights of distilled water, using a travelling microscope. The densities of solutions in cyclohexane were then determined by weighing and measuring the lengths of samples introduced into the tube. Molar volumes were calculated from density and concentration.[5]

$$\begin{array}{ccccc} \text{ester} & \longrightarrow & \text{ester} & \rightleftharpoons & \text{ester} \\ \text{(injection site)} & & \text{(blood)} & & \text{(fat)} \\ & & \downarrow \text{hydrolase} & & \\ & & \text{parent alcohol} & & \end{array} \qquad (3)$$

Discussion

Figure 2 shows the variation in the weight of levator ani with time, after injection of castrated rats with 1-mg doses of nandrolone nonanoate, and is typical of all the results obtained. Two peaks of activity were observed with all the esters and at all dose levels. Multiple regression analysis of the logarithms of times at which these maxima occurred (TM) against ethyl oleate–water distribution coefficients (P) gave correlations shown in eq 1 and 2. n represents the number of esters examined, r the correlation coefficient, and s the standard deviation. The figures in brackets in the equations represent the standard errors of coefficients and intercepts. F tests [$F_{1,4}$ = 0.69 and 2.75, respectively, α (0.05) = 7.71] indicated that neither correlation was improved by addition of a squared term in log P. Observed times of maximum effect for each ester agreed to the nearest whole day between dose levels. Observed and predicted times of maximum effect are given in Table II.

James, *et al.*,[6] have shown that the biological half-lives of the lower testosterone esters in rat are linearly related to ethyl oleate–water distribution coefficients, but half-lives at the injection site are not. As a result, they postulated a mechanism, which can be described diagramatically by eq 3. Equations 1 and 2 show that the times of the second maxima in the organ weight–time graphs correlate well with the distribution coefficient, but the correlation for the first maxima is not so good. It therefore appears from comparison with the observations cited above[6] that the first maximum in the organ weight–time plot represents the release of ester from the injection site and the second, the buildup of ester in the body fat and its subsequent release.

Ethyl oleate has been chosen as one of the distribution coefficient phases because it is the vehicle for injection; at the same time, it has a similar composition to body fat. The distribution coefficients quoted are approximate because they are actually the ratios of the solubilities in ethyl oleate and water. This procedure is open to criticism, but is the best estimate available, since the large difference between the solubilities in the two solvents makes the direct determination of the distribution coefficient extremely difficult. Evidence has been presented showing that the approximation used gives a good estimate of the variation in distribution coefficient from ester to ester.[7]

Anabolic activity was expressed as the area under the time–response graph (see Figure 2) and recorded in mg days. This was considered more appropriate for long-acting preparations than the increase in weight of levator ani, particularly since the latter was confused by the presence of two activity maxima. Results, corrected for control weights, for four dose levels are given in Table II. Each result is calculated from at least 32 determinations. Plots of log dose against log anabolic activity gave a series of parallel regression lines, indicating that the mechanism of action was similar throughout the homologous series and that the anabolic activities could be compared at equivalent doses. The results in Table II show that on a weight basis the butyrate has the lowest activity and the decanoate the highest. If anabolic activities are considered on the basis of nandrolone content, a similar pattern develops. Anabolic activities produced by 1-mM doses were calculated from the log dose–log anabolic activity plots. These are also given in Table II. Correlation of these results with the ethyl oleate–water distribution coefficients

Table II. Anabolic Activities and Times of Maximum Anabolic Effect of Nandrolone Esters

	Log distribution coeff	Log time of maximum effect: 1st maximum Obsd	1st maximum Calcd	2nd maximum Obsd	2nd maximum Calcd	Anabolic activity[a] (mg days) at dose (μg): 250	500	750	1000	Log anabolic activity for 1 mM dose: Obsd	Predicted
Butyrate	4.838	0.778	0.820	1.041	1.074	547 (162)	669 (224)	876 (133)	1488 (234)	2.783	2.776
Hexanoate	5.284	1.041	0.941	1.176	1.172	968 (413)	2142 (583)	2557 (519)	3731 (651)	3.163	3.174
Heptanoate	5.429	0.954	0.977	1.230	1.204	1079 (267)	3193 (583)	3463 (519)	6559 (449)	3.287	3.249
Octanoate	5.786	1.114	1.076	1.279	1.282	1063 (363)	2701 (348)	3856 (399)	5557 (395)	3.281	3.320
Nonanoate	5.658	0.954	1.042	1.279	1.254	1047 (576)	2509 (573)	2960 (684)	5080 (742)	3.264	3.313
Decanoate	5.904	1.146	1.108	1.322	1.308	1410 (541)	3192 (502)	4055 (509)	7735 (668)	3.409	3.307
Undecanoate	6.166	1.146	1.179	1.322	1.366	729 (271)	2470 (473)	3393 (365)	6576 (416)	3.192	3.216

[a] The figures in parentheses represent the 95% confidence limits of the results.

$$\log BR = 7.33\ (1.51)\log P - 0.636\ (0.138)(\log P)^2 - 17.8\ (4.1) \quad n = 7 \quad r = 0.970 \quad s = 0.064 \qquad (4)$$

$$F_{2,4} = 112.9\alpha\ (0.001) = 61.25$$

yielded eq 4 and the predicted activities given in Table II, indicating a binomial relationship between log anabolic activity (BR) and log distribution coefficient (P). The term in $(\log P)^2$ produced a significant improvement over the equivalent linear equation [$F_{1,4} = 16.3\alpha\ (0.025) = 12.22$].

Parabolic relationships of this type have been demonstrated for many systems by Hansch[8] who suggests that they represent movement of the drug from the point of application to the site of action. During its progress, a water-soluble drug will be obstructed by lipophilic barriers, and hydrophilic barriers will resist the passage of lipophilic drugs. The maximum in the parabola represents the optimum distribution coefficient somewhere between the two extremes. The good correlation in eq 4 indicates that the differences between the biological activities of the esters are largely due to this process. Confirmation is provided by the accuracy of the predicted anabolic activities in Table II.

Charton[9] has calculated inductive parameters (σ_I) from eq 5 where the pK_a applies to acetic acid substituted at the α carbon by the group to which the inductive parameter applies. σ_I values for the present series were estimated by insertion of the pK_a values of the appropriate normal fatty acids[10] into eq 5. Five of the pK_a values are identical and the whole seven of the acyl chains have a range in σ_I of only 0.025 ± 0.008. It is unlikely therefore that any difference in the inductive effects would contribute significantly to the variance in the biological results.

$$\sigma_I = -0.251\ pK_a + 1.186 \qquad (5)$$

Similar dependences on distribution coefficient can be shown with ring-substituted steroids. Huttenrauch and Keiner[11] measured the chloroform–glycerol distribution coefficients of a series of ring-substituted derivatives of 17α-methyltestosterone and compared them with anabolic activities. Anabolic activities were quoted for eight compounds, but distribution coefficients were determined for only six. We have estimated the remaining two distribution coefficients by assuming that the effects of substituent groups on the logarithm of the distribution coefficient of the parent compound are additive. Thus, for example, log P is 2.324 for 17α-methyltestosterone and 2.601 for 4-chloro-17α-methyltestosterone, giving a Δ log P for 4-chloro of 0.277. Mean values of Δ log P obtained by this process were 4-chloro, 0.166; 11-β-hydroxy, −0.360; 1(2)-dehydro, −0.166; yielding the estimated observed log P values given in Table III. Equation 6 was the best correlation obtained by multiple regression analysis of these results. Predicted anabolic activities are given in Table III. The correlation was not improved by inclusion of a squared term in log P [$F_{1,5} = 6.63\alpha\ (0.025) = 10.01$].

Huttenrauch and Scheffler[12] compared the anabolic activities of the same steroids with their R_m values, using various Bush systems. Their results, given in Table III, show fair correlation between the two properties. Equation 7 obtained with the system chloroform–methanol–water (2:1:1) is the best of these. Only seven compounds were considered because no R_m was quoted for testosterone. The correlation was not improved by inclusion of a squared term in R_m [$F_{1,4} = 1.49\alpha\ (0.05) = 7.71$]. It thus appears that much of the variance in intensity and duration of biological action of anabolic and androgenic steroids, resulting from changes in molecular structure, can be accounted for as variation in solubility behavior. This is probably the major factor in closely related groups of compounds, of which those considered above are examples, but when changes in structure are extensive or involve critical parts of the molecule, other factors probably become important.

The considerations outlined above may cast more light on accepted theories of structure–activity relationships of steroid hormones. Ringold,[13] for example, has developed a theory involving interaction between the α face of an androgen molecule and the receptor site and shown that groups positioned where they could sterically obstruct

$$\log BR = 6.95\ (1.78) - 2.09\ (0.83)\log P \quad n = 8 \quad r = 0.889 \quad s = 0.244 \qquad (6)$$

$$F_{1,6} = 18.98\alpha\ (0.01) = 13.74$$

$$\log BR = 2.35\ (0.11) + 0.829\ (0.239)\ R_m \quad 7 \quad 0.841 \quad 0.284 \qquad (7)$$

$$F_{1,5} = 80.07\alpha\ (0.001) = 47.18$$

Table III. Anabolic Activities of Ring-Substituted Derivatives of 17α-Methyltestosterone

			Log biological response[a,b]		
				Predicted	
	Log P	R_m	Obsd	Eq 6	Eq 7
17α-Methyltestosterone	2.324	−0.45	2.00	2.09	1.98
4-Chloro-17α-methyltestosterone	2.601	−0.71	1.70	1.51	1.76
1-Dehydro-17α-methyltestosterone	2.270	−0.26	2.10	2.21	2.14
1-Dehydro-4-chloro-17α-methyltestosterone	2.324	−0.55	1.81	2.09	1.90
4-Chloro-11β-hydroxy-17α-methyltestosterone	2.241	+0.22	2.60	2.27	2.53
11β-Hydroxy-17α-methyltestosterone	2.020[c]	+0.59	2.46	2.73	2.84
1-Dehydro-4-chloro-11β-hydroxy-17α-methyltestosterone	2.020[c]	+0.24	3.04	2.73	2.55
Testosterone	2.630		1.40	1.45	

[a]Relative to 17α-methyltestosterone, which is given the arbitrary value of 100%. [b]After oral administration to rats: R. Huttenrauch and K. Matthey, *Arch. Pharm. (Weinheim)*, **300**, 1007 (1967). [c]Estimated.

such an interaction cause a decrease in androgenic activity. James and Roberts[5] have demonstrated that solubilities in organic solvents can be dependent on the area of the α face available for contact with that of a neighboring molecule. This in turn influences the distribution coefficient. While not disagreeing in principle with Ringold's theory, it is suggested that separation of steric and solubility effects may lead to a better understanding of these structural requirements.

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Potential Psychotomimetics. 2.[1] Rigid Analogs of 2,5-Dimethoxy-4-methylphenylisopropylamine (DOM, STP)

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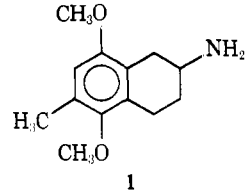
2-Amino-5,8-dimethoxy-6-methyl-1,2,3,4-tetrahydronaphthalene and 2-amino-4,7-dimethoxy-5-methylindan were prepared as rigid analogs of psychotomimetic phenylisopropylamines. Neither compound appeared to have psychotomimetic activity in rats. The effect of the aminotetralin derivative on 5-HT receptors in rat fundus strips and sheep umbilical arteries was also studied.

Early investigators studied 2-amino-1,2,3,4-tetrahydronaphthalene derivatives (aminotetralins) as lysergic acid congeners.[3,4] More recently, other workers have approached aminotetralins as rigid analogs of psychotomimetic phenylisopropylamines.[1,5,6] Cooper and Walters[7] found that for mescaline-like activity, racemic *trans*-2-(3,4,5-trimethoxyphenyl)cyclopropylamine was much more potent than the cis isomer. Although this finding supports a transoid conformation of the ethylamine side chain of psychotomimetics at the receptor, it does not indicate the relative conformation of the side chain with respect to the plane of the aromatic ring. Since 2,5-dimethoxy-4-methylphenylisopropylamine (DOM, STP) is a potent hallucinogen, it was decided to prepare and test compounds 1 (DOM-AT) and 2 (DOM-AI) to determine whether they possessed similar activity. Compound 1 was prepared by two independent routes, outlined in Schemes I and II, and the aminoindan derivative 2 was prepared as shown in Scheme III.

Examination of Dreiding models indicates that for 1 the distance from the center of the aromatic ring to the amino nitrogen is approximately 5.2 Å. When the nitrogen is in an axial conformation, it is approximately 1.3 Å above the plane of the ring, but when it is equatorial it lies nearly in the plane of the ring. For 2, which is a rigid structure, the Ar-N distance is about 4.6 Å and the nitrogen is about 1.2 Å above the plane of the aromatic ring. Thus, based on recently proposed correlations,[8,9] 1 would be predicted to most closely correspond to the structure of LSD.



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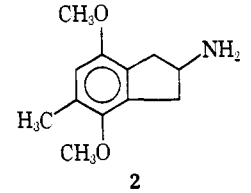

2

Experimental Section

A. Chemistry. All boiling points are uncorrected. Melting points were determined in open glass capillaries using a Thomas-Hoover Uni-Melt apparatus and are uncorrected. Elemental analyses were performed by Midwest Microlab Ltd., Indianapolis,