2.7 g of **3b** with 2 *N* HCl gave 1.7 g: mp 147–150°. Anal. ($C_{15}H_{21}NO_2$) C, H. The hydrochloride melted at 150–153°: $M^+$ 247 (73 mm), 204 (94 mm), 86 (14 mm). Anal. ($C_{15}H_{21}NO_2 \cdot HCl$) N.

**(2*RS*,6*SR*,11*SR*)-1,2,3,4,5,6-Hexahydro-6,11-dimethyl-2,6-methano-3-benzazocine-8,11-diol (3d).** Demethylation of 4.1 g of **3c** by 15 min of refluxing with 40 ml of 48% HBr gave a 68% yield of **3d**: mp 268.5–270° from MeOH–$Et_2O$; $M^+$ 233 (57 mm), 190 (63 mm), 86 (13 mm), 43 (91 mm). Anal. ($C_{14}H_{19}NO_2$) C, H, N.

**(2*RS*,6*SR*,11*SR*)-1,2,3,4,5,6-Hexahydro-6,11-dimethyl-3-(3-methyl-2-butenyl)-2,6-methano-3-benzazocine-8,11-diol Hydrochloride (3, $R_3$ = dimethylallyl; $R_8$ = H).** Alkylation of **3d** with 3-methyl-2-butenyl bromide in DMF gave the product isolated as the hydrochloride: mp 215–218° dec (*i*-PrOH–$Me_2CO$). Anal. ($C_{19}H_{27}NO_2 \cdot HCl$) C, H, Cl.

**(2*RS*,6*SR*,11*SR*)-3-Cyclopropylmethyl-1,2,3,4,5,6-hexahydro-6,11-dimethyl-2,6-methano-3-benzazocine-8,11-diol Hydrochloride Sesquihydrate (3, $R_3$ = cyclopropylmethyl; $R_8$ = H).** A solution of 1.94 g of **3d** in 35 ml of warm pyridine was treated with 1.40 g of cyclopropanecarbonyl chloride. The crude ester (2.8 g) was reduced ($LiAlH_4$, THF) and isolated as the HCl (1.84 g). An analytical sample from MeOH–$Et_2O$ melted at 164–167°: $M^+$ 287 (52 mm), 246 (83 mm), 244 (54 mm), 140 (9 mm), 55 (73 mm). Anal. ($C_{18}H_{25}NO_2 \cdot HCl \cdot 1.5H_2O$) C, H, N.

The same product was obtained from **3d** and cyclopropylmethyl bromide.

**Acknowledgments.** We are indebted to Mrs. Anne K. Pierson for pharmacological test results and to Mrs. Susan J. Killeen and Mr. Allan Hlavac of Dr. R. K. Kullnig's laboratory for mass spectral data.

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(4) S. Saito and E. L. May, *J. Org. Chem.*, **26**, 4536 (1961).
(5) The benzomorphan nomenclature has been used in the introduction since most workers in the field prefer it even though it has led to errors in Chemical Abstracts. The C.A. nomenclature has been used in the Experimental Section.
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(9) Where analyses are indicated only by symbols of the elements, analytical results obtained for those elements were within ±0.4% of the theoretical values. Melting points are not corrected for emergent stem errors.
(10) The 11*SR* compounds correspond to May's $\alpha$ isomers and have the OH oriented toward the nitrogen.
(11) Prepared but not characterized by May and coworkers.
(12) We are indebted to Mr. Stanley Laskowski for the preparation of this starting material.

# Quantitative Structure–Activity Relationships in the $\Delta^6$-6-Substituted Progesterone Series. A Reappraisal

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A quantitative structure–activity analysis concerning the progestational activity of a series of $\Delta^6$-6-substituted progesterones is presented which differs from that published recently by other authors. In the current study all compounds in the data set for which parameters are available are included and activity is shown to relate to primarily lipophilic but also steric effects.

A recent article by Wolff and Hansch[1] presented an analysis of quantitative structure–activity relationships in the $\Delta^6$-6-substituted progesterone series. This analysis utilized activity data published by Teutsch et al.[2] The latter authors had discussed structure–activity relationships in this series primarily in terms of steric effects.

Wolff and Hansch presented eq 1 and 2 as those which accounted most satisfactorily for the variation of activity in the series. Of these they were inclined to favor eq 2. A striking feature of the Wolff and Hansch article was that their correlations were derived using a data set from which the most active member of the series, the 6-methyl compound, had been excluded. This exclusion was justified on the grounds that the activity of the 6-methyl compound was very poorly predicted by eq 1 and 2 (off by 4 standard deviations) and it was further stated that the failure of the 6-methyl compound to fit these equations "is a clear indication that the methyl group is acting by a different mechanism from all other substituents". However, no convincing evidence or explanation of why the mechansim should be different was presented.

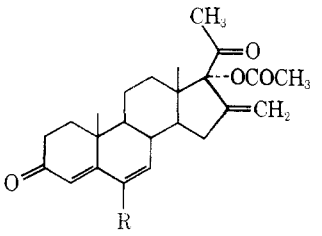
Wolff and Hansch did not discuss any correlation equations based on the complete data set. In the present study the complete data set (Table I) has been used in a multiple regression analysis in conjunction with the substituent parameters $\pi$, representing possible hydrophobic bonding and penetration effects,[3] $\mathcal{F}$ and $\mathcal{R}$ for electronic field and resonance effects,[4] and MR and *C* as alternative measures of substituent size. MR is a crude measure of substituent bulk which contains some electronic contributions.[5] *C* is the circumference of the circle circumscribed by the substituent and was employed by Teutsch et al.[2] for structure–activity correlations in the $\Delta^6$-6-substituted progesterone series.

An examination of single parameter equations reveals $\pi$ to be the dominant single variable, which alone accounted for 58% of the variance in the data (eq 3). This result is consistent with the findings of Wolff and Hansch. The steric measures *C* and MR also showed some degree of correlation accounting for 37 and 22% of the data variance, respectively. No correlation was observed with the electronic terms.

The best correlation was obtained using the two-parameter eq 4 involving $\pi$ and the steric term *C*.[6] This equation has high statistical significance, satisfying the *F* test at the 0.005 level, and accounts for 73% of the variance in the data. The $\pi$ term is significant at the 0.005 level and the *C* term at the 0.05 level. The correlation could not be improved by the addition of other variables. Using the term MR instead of *C* yields eq 5. However, in this case the MR term is significant only at the 0.25 level.

The data fit for eq 4 ($r^2$ = 0.73, $s$ = 0.54) is only slightly inferior to that for eq 2 proposed by Wolff and Hansch ($r^2$

**Table I.** Progestational Activity and Substituent Constants of Progesterone Derivatives




| R | Obsd rel act.[a] | Calcd rel act.[b] | Calcd rel act.[c] | Obsd log A | Calcd log A[b] | Calcd log A[c] | $\pi$[f] | $\mathcal{F}$[f] | $\mathcal{R}$[f] | MR[f] | $C$[g] | Calcd rel act.[d] | Calcd rel act.[e] |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| $CH_3$ | 91 | 26 | 26 | 1.96 | 1.41 | 1.42 | 0.56 | −0.04 | −0.13 | 5.65 | 8.67 | 1.7 | 0.9 |
| Cl | 77 | 50 | 36 | 1.89 | 1.70 | 1.56 | 0.71 | 0.41 | −0.15 | 6.03 | 6.09 | 48 | 30 |
| F | 55 | 17 | 19 | 1.74 | 1.23 | 1.27 | 0.14 | 0.43 | −0.34 | 0.92 | 4.27 | 36 | 28 |
| Br | 42 | 62 | 34 | 1.62 | 1.79 | 1.53 | 0.86 | 0.44 | −0.17 | 8.88 | 7.09 | 51 | 31 |
| $N_3$ | 20 | 47 | 10 | 1.30 | 1.67 | 1.01 | 0.46 | 0.30 | −0.13 | 10.20 | 15.64 | 6.8 | 14 |
| OMe | 14 | 30 | 4.4 | 1.15 | 0.48 | 0.64 | −0.02 | 0.26 | −0.51 | 7.87 | 15.13 | 2.6 | 5.1 |
| SCN | 12 | 10 | 5.6 | 1.08 | 1.03 | 0.75 | 0.41 | 0.36 | 0.19 | 13.40 | 12.94 | 5.2 | 22 |
| $CF_3$ | 11 | 35 | 65 | 1.04 | 1.55 | 1.81 | 0.88 | 0.38 | 0.19 | 5.02 | 11.93 | 68 | 19 |
| CN | 6 | 3.1 | 1.4 | 0.78 | 0.49 | 0.14 | −0.57 | 0.51 | 0.19 | 6.33 | 4.84 | 5.0 | 4.5 |
| OEt | 1 | 2.7 | 6.0 | 0.00 | 0.43 | 0.78 | 0.38 | 0.22 | −0.44 | 12.47 | 23.42 | 0.4 | 7.1 |
| H | 1 | 15 | 13 | 0.00 | 1.19 | 1.11 | 0.00 | 0.00 | 0.00 | 1.03 | 2.32 | 1.5 | 0.7 |
| CHO | 1 | 1.3 | 1.0 | 0.00 | 0.13 | 0.02 | −0.65 | 0.31 | 0.13 | 6.88 | 9.92 | 1.0 | 0.6 |
| OAc | 0.2 | 0.3 | 0.5 | −0.70 | −0.58 | −0.33 | −0.64 | 0.41 | −0.07 | 12.47 | 23.36 | 0.8 | 1.4 |
| NHAc | 0.1 | 0.1 | 0.1 | −1.00 | −0.93 | −0.85 | −0.97 | 0.28 | −0.26 | 14.93 | 23.67 | 0.1 | 0.1 |

[a]Relative activity (progesterone = 1) from ref 2. [b]Calculated using eq 4. [c]Calculated using eq 5. [d]Calculated using eq 1. [e]Calculated using eq 2. [f]Values from ref 5. [g]Values from ref 2.

| | $n$ | $s$ | $r^2$ | $r$ | |
|---|---|---|---|---|---|
| $\log A = 0.26\ (\pm1.01) - 0.07\ (\pm0.07)$ MR + $0.97\ (\pm0.53)\ \pi + 2.84\ (\pm2.50)\ \mathcal{F}$ | 13 | 0.49 | 0.80 | 0.89 | (1) |
| $\log A = -0.17\ (\pm0.88) + 1.06\ (\pm0.52)\ \pi + 3.46\ (\pm2.68)\ \mathcal{F} - 1.05\ (\pm1.11)\ \pi^2$ | 13 | 0.49 | 0.79 | 0.89 | (2) |
| $\log A = 0.64\ (\pm0.38) + 1.20\ (\pm0.65)\ \pi$ | 14 | 0.65 | 0.58 | 0.76 | (3) |
| $\log A = 1.32\ (\pm0.68) + 1.00\ (\pm0.57)\ \pi - 0.05\ (\pm0.04)\ C$ | 14 | 0.54 | 0.73 | 0.86 | (4) |
| $\log A = 1.18\ (\pm0.81) + 1.09\ (\pm0.64)\ \pi - 0.07\ (\pm0.09)$ MR | 14 | 0.61 | 0.66 | 0.81 | (5) |
| $\log A = 1.75\ (\pm0.53) + 0.86\ (\pm0.40)\ \pi - 0.08\ (\pm0.04)\ C$ | 13 | 0.37 | 0.88 | 0.94 | (6) |
| $\log A = 1.70\ (\pm0.35) + 0.96\ (\pm0.51)\ \pi - 0.11\ (\pm0.09)$ MR | 13 | 0.48 | 0.80 | 0.89 | (7) |

= 0.79, $s$ = 0.49) while eq 4 employs one less variable, but most important it is not dependent on the removal of any compound from the data set.

That the slightly better data fit shown by eq 2 is not meaningful can be demonstrated by the exclusion of the 6-H compound from the data set with the 6-methyl compound included. From this set eq 6 may be derived which not only shows a better statistical fit than the Wolff and Hansch equation but employs one less variable. Substituting MR for $C$ yields eq 7 with a statistical fit about equivalent to eq 2. This example serves to illustrate the pitfalls of removing a compound from the data set. There is no more or less reason to omit the 6-H than the 6-methyl compound and there is no adequate reason from the available data why any compound in the series should be treated in a special way and dropped from the data set. Thus, the assertion by Wolff and Hansch that the 6-methyl compound, because it does not fit eq 1 and 2, is acting by a different mechanism from all of the other substituents is not warranted.

In the view of the present authors the available data are best accounted for by eq 4, a simple two-term relationship where one term has the effect of enhancing activity as the lipophilicity of the substituent is increased and the second term of decreasing activity with increased substituent size. The $C$ or MR terms and a $\pi^2$ term each have the effect of reducing the activity contribution of a substituent. In a larger data set containing some substituents with higher $\pi$ values which allow discrimination from the steric effect, the $\pi^2$ term might well become a significant variable. A $\pi$–$\pi^2$ type relationship would be expected for in vivo biological data.

In terms of predicting the activity of new compounds the 6-$SO_2C_6H_5$ analog, expected to be highly active (relative activity 95) on the basis of the preferred equation (eq 2) of Wolff and Hansch,[1] would be projected as having very low activity (relative activity 0.4) according to eq 4. Also, the 6-$CH_2CH_3$ analog which would be expected to have a very low activity according to both eq 1 and 2 of Wolff and Hansch (relative activities 2.5 and 0.4, respectively) is predicted to be a moderately potent compound (relative activ-

ity 22) by eq 4 from the present study.

**Acknowledgment.** The authors are indebted to Mr. R. J. Costello of the Department of Computer and Information Sciences for the statistical studies.

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(6) Use of an alternate steric measure, a half-sphere volume, described by Teutsch et al.,[2] gives an equation of the same form and an almost identical statistical fit.

# 4-Amino-5-arylpyrimidines as Antiinflammatory Agents

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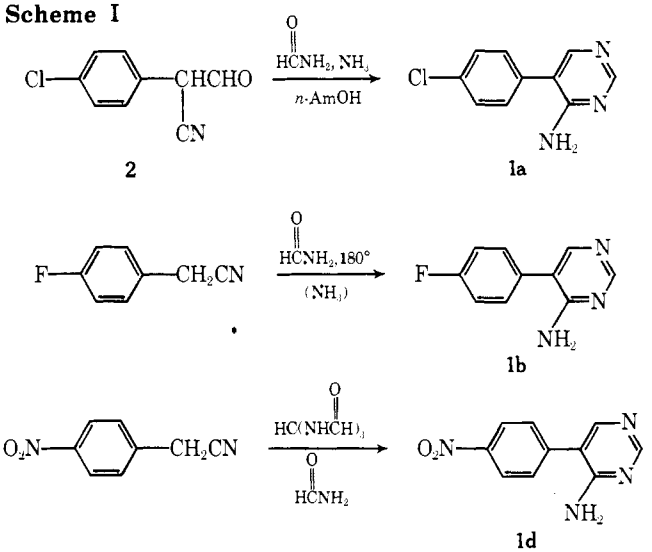
4-Amino-5-arylpyrimidines were synthesized by a variety of methods and have demonstrated antiinflammatory activity in the carrageenan-induced edema in the rat but displayed little activity against adjuvant-induced arthritis in rats or against uv-induced erythema in guinea pigs.

4-Amino-5-(*p*-chlorophenyl)pyrimidine (**1a**), which was obtained as a side product in a chemical sequence, was found to possess antiinflammatory activity in the rat carrageenan edema test. The title compounds, 4-amino-5-arylpyrimidines (**1**), were prepared by a variety of methods.[1-4] The treatment of phenylcyanoacetaldehydes (**2**) with formamide in refluxing *n*-amyl alcohol in a stream of $NH_3$ or with excess formamide at 170–179° gave **1** as the predominate product.[2] Other methods used involved heating of arylacetonitriles with excess formamide,[1] sometimes in a stream of $NH_3$,[3] producing moderate yields of **1**. Tris(formamino)methane[4-6] when reacted at 190° with arylacetonitriles gave good yields of 4-amino-5-arylpyrimidines[4] (Scheme I). The monoacylpyrimidine **4b** was obtained by refluxing **1e** in acetic acid–acetic anhydride.[2,3] The diacetylpyrimidine **4a** was obtained by heating **1a** in acetic anhydride–pyridine[2,3] on a steam bath.

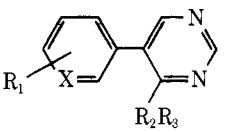
**Scheme I**




**Pharmacology.** The mono- and diacyl derivatives of several pyrimidines were prepared and were also active in the carrageenan-induced edema in the rat but also lacked activity in follow-up tests.

The acute antiinflammatory activity of the pyrimidines was determined using Royal Hart, Wistar strain rats. The differences in edema were considered to be due to drug efficacy and are expressed as a control (C)/treated (T) (untreated/treated) efficacy ratio (the ratio of mean edema of eight control animals which did not receive drugs over the mean edema of two treated rats). If the C/T ratio is equal to or greater than 1.41, the test was repeated with two additional rats. If the mean C/T in the four rats is equal to or greater than 1.43 the compound was accepted as active. The results are summarized in Table I.

Table I. Carrageenan-Induced Edema in the Rat




| Compd | $R_1$ | $R_2$ | $R_3$ | X | C/T[a] |
|---|---|---|---|---|---|
| 1a | *p*-Cl | $NH_2$ | | CH | 1.93 |
| 1b | *p*-F | $NH_2$ | | CH | 1.83 |
| 1c | *p*-$CH_3$ | $NH_2$ | | CH | 2.24 |
| 1d | *p*-$NO_2$ | $NH_2$ | | CH | <1.43 |
| 1e | H | $NH_2$ | | CH | 5.10 |
| 1f | *p*-Ph | $NH_2$ | | CH | <1.43 |
| 1g | *o*-$CH_3$ | $NH_2$ | | CH | 3.28 |
| 1h | *m*-$CH_3$ | $NH_2$ | | CH | 3.99 |
| 1i | *m*-F | $NH_2$ | | CH | <1.43 |
| 1j | *m*-$CF_3$ | $NH_2$ | | CH | <1.43 |
| 1k | *m*-Cl | $NH_2$ | | CH | 2.52 |
| 1l | *o*-Cl | $NH_2$ | | CH | 2.61 |
| 1m | 2,4-$Cl_2$ | $NH_2$ | | CH | <1.43 |
| 1n | *p*-Br | $NH_2$ | | CH | 2.35 |
| 3a | *p*-Cl | NAc | Ac | CH | 1.95 |
| 3b | H | H | NAc | CH | 3.71 |
| 4a | | OH | | CH | 2.55 |
| 4b | | $NH_2$ | | N | <1.43 |
| Controls (historical) | | | | | 1.00 |
| Aspirin | | | | | 2.83 |

[a] Mean value (average value of four rats).

The carrageenan-induced edema is a general test for the discovery of antiarthritic agents[7] but is nonspecific and a large number of miscellaneous drugs with varying pharma-