Palmitoyl chloride (49 g, 0.178 mol) was dissolved in 500 ml of ether and cooled to 0°, and 500 ml of 30% H_2O_2 was added dropwise. After the solution was stirred for 20 min, 50 ml of pyridine was added, and the resulting solution was stirred for an additional 30 min at room temperature. The ether layer was washed with 250 ml of 5% HCl, water, and 2% NaOH, dried over $MgSO_4$, and evaporated: yield 30 g (62%).

6-Hydroxy-4,7-dioxobenzothiazole (4.0 g, 0.022 mol) was dissolved in 500 ml of acetic acid. The temperature was raised to 90°, and palmitoyl peroxide (16 g, 0.031 mol) in 300 ml of ether was added over a 4-hr period. The solution was filtered to give 1.7 g of starting material. The filtrate was stirred overnight, and the solvent was evaporated. The remaining oil was placed on a silica gel column and eluted with ether. The yellow fractions were combined, and the solvent was removed. Two recrystallizations from hexane–ether gave 0.32 g of orange solid (6.5%): mp 129–130°; nmr ($CDCl_3$) δ 0.90, 1.26 (m, 29 H), 2.61 (t, 2 H), 9.16 (s, 1 H). *Anal.* $C_{22}H_{33}NO_3S$) C, H, N.

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References

(1) T. H. Porter, F. S. Skelton, and K. Folkers, *J. Med. Chem.*, 14, 1029 (1971).
(2) F. S. Skelton, P. J. Rietz, and K. Folkers, *ibid.*, 13, 602 (1970).
(3) C. M. Bowman, F. S. Skelton, T. H. Porter, and K. Folkers, *ibid.*, 16, 206 (1973).
(4) H. H. Fox and M. T. Bogert, *J. Amer. Chem. Soc.*, 61, 2013 (1939).
(5) L. Fieser and M. Fieser, "Reagents for Organic Synthesis," Wiley, New York, N. Y., 1967, p 4.
(6) H. H. Hodgson and A. P. Mahadevan, *J. Chem. Soc.*, 325 (1947).
(7) L. Rane and D. S. Rane, *Proc. Helminthol. Soc. Washington*, 39, 283 (1972).

Acute Oral Toxicity of 2-Alkyl- and 2,6-Dialkylanilines. Correlation with Lipophilicity

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Jacobson[1] has recently presented data pertaining to the acute rat oral toxicity of a group of 2-alkyl- and 2,6-dialkylaniline derivatives. Also presented was a very brief discussion of the structure–activity relationships which may be operative in this series.

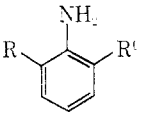
A high correlation (r = 0.926) has now been found between these toxicity data and the partition coefficients (P)[2] of the corresponding anilines. Regression of the acute oral data against log P provided a relationship which accounted for 85.9% of the observed variation in data. Inclusion of a parameter (E_s)[3,4] related to the steric requirement of the ortho substituents(s) did not significantly change the accountability of eq 1. The correlation (r =

$$\log 1/C = 2.551 - 0.274 \log P \qquad (1)$$

$s = 0.0503$; $MR^2 = 0.8586$; $F = 36.45$; $r = 0.926$

0.775, accountability 60.1%) between E_s and log $1/C$ was also significantly less than that observed with P. It should be noted that the correlation between P and E_s for these compounds is quite high (r = 0.894); about 80% of the variation in P is accounted for by the variation in E_s. Although there may be steric effects influencing the activity of these compounds, the high correlation with P suggests that relative lipophilicity (P) is probably the primary toxicity determinative. If other than alkyl substituents were included in the series almost certainly electronic or steric effects would begin to play a role along with lipophilicity. The importance of P may reflect a lipophilicity-related *in vivo* distribution effect[5] and/or a direct relationship between lipophilicity and *in vivo* degradation (metabolism, conjugation)[6] for these materials.

Table I. Structural Parameters and Observed and Calculated Toxicity Values



No.	R	R¹	Log P	E_s, R,R¹	Rat peroral LD_{50} values, g/kg Obsd	Calcd
1	H	H	0.90[a]	2.48	0.44	0.46
2	H	CH_3	1.30[a]	1.24	0.90	0.68
3	CH_3	CH_3	1.70	0	0.84	1.0
4	H	C_2H_5	1.80	1.07	1.26	1.06
5	C_2H_5	C_2H_5	2.70	−0.14	2.69	2.31
6	H	$CH(CH_3)_2$	2.10	0.75	1.18	1.43
7	$CH(CH_3)_2$	$CH(CH_3)_2$	3.30	−0.98	4.27	4.00
8	CH_3	C_2H_5	2.20	−0.07	1.18	1.52

[a] From ref 2; the remainder was calculated by standard methods.

The data employed in this study are recorded in Table I together with the calculated toxicities from eq 1. Log $1/C$ in eq 1 is calculated by eq 2.

$$\log 1/C = -\left[\log \frac{100 \times LD_{50}}{\text{mol wt}}\right] + 2 \qquad (2)$$

References

(1) K. H. Jacobson, *Toxicol. Appl. Pharmacol.*, 22, 153 (1972).
(2) A. Leo, C. Hansch, and D. Elkins, *Chem. Rev.*, 71, 525 (1971).
(3) E. Kutter and C. Hansch, *J. Med. Chem.*, 12, 647 (1969).
(4) P. N. Craig, *ibid.*, 14, 680 (1971).
(5) C. Hansch and W. J. Dunn, III, *J. Pharm. Sci.*, 61, 1 (1972).
(6) C. Hansch, *Drug Metab. Rev.*, 1, 1 (1972).